CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74751

APPROVAL LETTER

ANDA 74-751

SEP 30

Chelsea Laboratories, Inc.
Attention: Ernest E. Lengle, Ph.D.
8606 Reading Road
P.O. Box 15686
Cincinnati, Ohio 45215-0686

Dear Sir:

This is in reference to your abbreviated new drug application dated September 19, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Clomipramine Hydrochloride Capsules, 25 mg, 50 mg, and 75 mg.

Reference is also made to your amendments dated February 13, March 15, May 28, and December 17, 1996; January 1 and 20, June 6, July 23, August 10, 11, 17, and 20, and December 18, 1997; and February 27, July 6, and September 10, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Clomipramine Hydrochloride Capsules, 25 mg, 50 mg, and 75 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Anafranil® Capsules 25 mg, 50 mg, and 75 mg, respectively, of Novartis Pharmaceuticals Corporation). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed

materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ for 9-30-98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

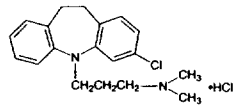
74751

DRAFT FINAL PRINTED LABELING

DESCRIPTION

Clomipramine hydrochloride is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3. The molecular formula is $C_{19}H_{24}Cl_2N_2$.

Each capsule, for oral administration, contains 25, 50, or 75 mg of clomipramine hydrochloride. In addition, each capsule contains the following inactive ingredients: black iron oxide (25 mg only), colloidal silicon dioxide, FD&C blue #1 (50 mg only), gelatin, magnesium stearate, pregelatinized starch, red iron oxide (25 mg only), silicon dioxide, sodium lauryl sulfate, titanium dioxide and yellow iron oxide (25 mg only). The imprinting ink contains D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Red No. 40 Aluminum Lake and synthetic black iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's capacity to inhibit the reuptake of serotonin (5-HT) is thought to be important.

Pharmacokinetics

Absorption/Bioavailability: CMI from clomipramine hydrochloride capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations (C_{SS}) and area-under-plasma-concentration-time curves (AUC) of CMI and CMI's major active metabolite, desmethylclomipramine (DMI), were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although (C_{SS}) and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and CMI/DMI concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_{SS} and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/mL to 154 ng/mL (mean, 92 ng/mL). After multiple daily doses of 150 mg of clomipramine hydrochloride, steady-state maximum plasma concentrations range from 94 ng/mL to 339 ng/mL (mean, 218 ng/mL) for CMI and from 134 ng/mL to 532 ng/mL (mean, 274 ng/mL) for DMI. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

Distribution: CMI distributes into cerebrospinal fluid (CSF) and brain and into breast milk. DMI also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of CMI is approximately 97%, principally to albumin, and is independent of CMI concentration. The interaction between CMI and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

Metabolism: CMI is extensively biotransformed to DMI and other metabolites and their glucuronide conjugates. DMI is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of CMI in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of CMI and DMI were only about 0.8-1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination: Evidence that the C_{SS} and AUC for CMI and DMI may increase disproportionately with increasing oral doses suggests that the metabolism of CMI and DMI may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of CMI and DMI are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of clomipramine hydrochloride have not been determined.

Interactions: Coadministration of haloperidol with CMI increases plasma concentrations of CMI. Coadministration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated CMI better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of CMI were significantly lower in smokers than in nonsmokers.

INDICATIONS AND USAGE

Clomipramine hydrochloride is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of clomipramine hydrochloride for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking CMI experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. CMI treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of clomipramine hydrochloride for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use clomipramine hydrochloride for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Clomipramine HCl Capsules

KJ

KJ

Clomipramine HCl Capsules

CONTRAINDICATIONS

Clomipramine hydrochloride is contraindicated in patients with a history of hypersensitivity to clomipramine hydrochloride or other tricyclic antidepressants.

Clomipramine hydrochloride should not be given in combination, or within 14 days before or after treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Clomipramine hydrochloride is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS

Seizures

During premarket evaluation, seizure was identified as the most significant risk of clomipramine hydrochloride use.

The observed cumulative incidence of seizures among patients exposed to clomipramine hydrochloride at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates correct the crude rate of 0.7% (25 of 3519 patients) for the variable duration of exposure in clinical trials.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of CMI greater than 250 mg is limited, given that the plasma concentration of CMI may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Caution should be used in administering clomipramine hydrochloride to patients with a history of seizures or other predisposing factors, e.g., brain damage or varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Rare reports of fatalities in association with seizures have been reported by foreign post-marketing surveillance, but not in U.S. clinical trials. In some of these cases, clomipramine hydrochloride had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions. Thus a causal association between clomipramine hydrochloride treatment and these fatalities has not been established.

Physicians should discuss with patients the risk of taking clomipramine hydrochloride while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

PRECAUTIONS

General

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for clomipramine hydrochloride should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects: Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking clomipramine hydrochloride in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion, And Other Neuropsychiatric Phenomena: Patients treated with clomipramine hydrochloride have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with clomipramine hydrochloride. As with tricyclic antidepressants to which it is closely related, clomipramine hydrochloride may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

Mania/Hypomania: During premarketing testing of clomipramine hydrochloride in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to clomipramine hydrochloride.

Hepatic Changes: During premarketing testing, clomipramine hydrochloride was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes: Although no instances of severe hematologic toxicity were seen in the premarketing experience with clomipramine hydrochloride, there have been postmarketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with clomipramine hydrochloride use. As is the case with tricyclic antidepressants

to which clomipramine hydrochloride is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with clomipramine hydrochloride.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when clomipramine hydrochloride was used in combination with other drugs. When clomipramine hydrochloride and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction: The rate of sexual dysfunction in male patients with OCD who were treated with clomipramine hydrochloride in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes: In controlled studies of OCD, weight gain was reported in 18% of patients receiving clomipramine hydrochloride, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving clomipramine hydrochloride had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving clomipramine hydrochloride and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy: As with closely related tricyclic antidepressants, concurrent administration of clomipramine hydrochloride with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Surgery: Prior to elective surgery with general anesthetics, therapy with clomipramine hydrochloride should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use in Concomitant Illness: As with closely related tricyclic antidepressants, clomipramine hydrochloride should be used with caution in the following:

(1) Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity;

(2) Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug;

(3) Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises;

(4) Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of clomipramine hydrochloride, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthemia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of clomipramine hydrochloride have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe clomipramine hydrochloride:

(1) The risk of seizure (see WARNINGS);

(2) The relatively high incidence of sexual dysfunction among males (see Sexual Dysfunction);

(3) Since clomipramine hydrochloride may impair the mental and/or physical abilities required for the performance of complex tasks, and since clomipramine hydrochloride is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS);

(4) Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since clomipramine hydrochloride may exaggerate their response to these drugs;

(5) Patients should notify their physician if they become pregnant or intend to become pregnant during therapy;

(6) Patients should notify their physician if they are breast-feeding.

Drug Interactions

The risks of using clomipramine hydrochloride in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of clomipramine hydrochloride, caution is advised in using it concomitantly with other CNS-active drugs (see Information for Patients). Clomipramine hydrochloride should *not* be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when clomipramine hydrochloride is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with CMI because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of methylphenidate or hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin), and such an effect may be anticipated with CMI as well. Administration of CMI has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Interactions).

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7%-10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asians, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary). Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either tricyclic antidepressant or the other drug. Furthermore, whenever one of these drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

Because clomipramine hydrochloride is highly bound to serum protein, the administration of clomipramine hydrochloride to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clomipramine hydrochloride by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

Pregnancy: Teratogenic Effects; Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken clomipramine hydrochloride until delivery. Clomipramine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Clomipramine hydrochloride has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received clomipramine hydrochloride for up to 8 weeks. In addition, 150 adolescent patients have received clomipramine hydrochloride in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14-17 years of age. While the adverse reaction profile in this age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with clomipramine hydrochloride may have on the growth and development of children.

The safety and effectiveness in pediatric patients below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of clomipramine hydrochloride in pediatric patients under the age of 10.

Use in Elderly

Clomipramine hydrochloride has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in U.S. clinical trials received clomipramine hydrochloride for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

ADVERSE REACTIONS

Commonly Observed

The most commonly observed adverse events associated with the use of clomipramine hydrochloride and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3616 patients who received clomipramine hydrochloride in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%) primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received clomipramine hydrochloride in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving clomipramine hydrochloride (N=322) or placebo (N=319) or children treated with clomipramine hydrochloride (N=46) or placebo (N=44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics, and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Clomipramine Hydrochloride

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials (Percentage of Patients Reporting Event)

	Adults		Children and Adolescents	
Body System/ Adverse Event*	**Clomipramine Hydrochloride (N=322)**	**Placebo (N=319)**	**Clomipramine Hydrochloride (N=46)**	**Placebo (N=44)**
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Dizziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7
Libido change	21	3	-	-
Nervousness	18	2	4	2
Myoclonus	13	-	2	-
Increased appetite	11	2	-	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	-
Twitching	7	1	4	5
Impaired concentration	5	2	-	-
Depression	5	1	-	-
Hypertonia	4	1	2	-
Sleep disorder	4	-	9	5
Psychosomatic disorder	3	-	-	-
Yawning	3	-	-	-
Confusion	3	-	2	-
Speech disorder	3	-	-	-
Abnormal dreaming	3	-	-	2
Agitation	3	-	-	-

Migraine	3	-	-	-
Depersonalization	2	-	2	-
Irritability	2	2	2	-
Emotional lability	2	-	-	2
Panic reaction	1	-	2	-
Aggressive reaction	-	-	2	-
Paresis	-	-	2	-
Skin and Appendages				
Increased sweating	29	3	9	-
Rash	8	1	4	2
Pruritus	6	-	2	2
Dermatitis	2	-	-	2
Acne	2	2	-	5
Dry skin	2	-	-	5
Urticaria	1	-	-	-
Abnormal skin odor	-	-	2	-
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	-	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	-
Flatulence	6	3	-	2
Tooth disorder	5	-	-	-
Gastrointestinal disorder	2	-	-	2
Dysphagia	2	-	-	-
Esophagitis	1	-	-	2
Eructation	-	-	2	-
Ulcerative stomatitis	-	-	2	-
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	18	1	2	-
Flushing	8	-	7	-
Hot flushes	5	-	2	-
Chest pain	4	4	7	-
Fever	4	-	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	-	-
Chills	2	1	-	-
Weight decrease	-	-	7	-
Otitis media	-	-	4	5
Asthenia	-	-	2	-
Halitosis	-	-	2	-
Cardiovascular System				
Postural hypotension	6	-	4	-
Palpitation	4	2	4	-
Tachycardia	4	-	2	-
Syncope	-	-	2	-
Respiratory System				
Pharyngitis	14	9	-	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Bronchospasm	2	-	7	2
Epistaxis	2	-	-	2
Dyspnea	-	-	2	-
Laryngitis	-	1	2	-

Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	-	-
Micturition frequency	5	3	-	-
Urinary retention	2	-	7	-
Dysuria	2	2	-	-
Cystitis	2	-	-	-
Female Patients Only	**(N=182)**	**(N=167)**	**(N=18)**	**(N=21)**
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	-	-	-
Menstrual disorder	4	2	-	-
Vaginitis	2	-	-	-
Leukorrhea	2	-	-	-
Breast enlargement	2	-	-	-
Breast pain	1	-	-	-
Amenorrhea	1	-	-	-
Male Patients Only	**(N=148)**	**(N=152)**	**(N=36)**	**(N=23)**
Ejaculation failure	42	2	6	-
Impotence	20	3	-	-
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	-	4	-
Tinnitus	6	-	4	-
Abnormal lacrimation	3	2	-	-
Mydriasis	2	-	-	-
Conjunctivitis	1	-	-	-
Anisocoria	-	-	2	-
Blepharospasm	-	-	2	-
Ocular allergy	-	-	2	-
Vestibular disorder	-	-	2	2
Musculoskeletal				
Myalgia	13	9	-	-
Back pain	6	6	-	-
Arthralgia	3	5	-	-
Muscle weakness	1	-	2	-
Hemic and Lymphatic				
Purpura	3	-	-	-
Anemia	-	-	2	2
Metabolic and Nutritional				
Thirst	2	2	-	2

* Events reported by at least 1% of clomipramine hydrochloride patients are included.

Other Events Observed During the Premarketing Evaluation of Clomipramine Hydrochloride

During clinical testing in the U.S., multiple doses of clomipramine hydrochloride were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized events categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to clomipramine hydrochloride who experienced an event of the type cited on at least one occasion while receiving clomipramine hydrochloride. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with clomipramine hydrochloride, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: *Infrequent* - general edema, increased susceptibility to infection, malaise. *Rare* - dependent edema, withdrawal syndrome.

Cardiovascular System: *Infrequent* - abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* - aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: *Infrequent* - abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* - cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: *Infrequent* - hypothyroidism. *Rare* - goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: *Infrequent* - lymphadenopathy. *Rare* - leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: *Infrequent* - dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare* - fat intolerance, glycosuria.

Musculoskeletal System: *Infrequent* - arthrosis. *Rare* - dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System: *Frequent* - abnormal thinking, vertigo. *Infrequent* - abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. *Rare* - anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

Respiratory System: *Infrequent* - bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* - cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: *Infrequent* - alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* - chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: *Infrequent* - abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* - blepharitis, chromatopsia, conjuctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: *Infrequent* - endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* - albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE

Clomipramine hydrochloride has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with clomipramine hydrochloride discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential clomipramine hydrochloride abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received clomipramine hydrochloride for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for clomipramine hydrochloride in foreign marketing, it is not possible to predict the extent to which clomipramine hydrochloride might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic overdose. Therefore, hospital monitoring is required as soon as possible.

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with clomipramine hydrochloride either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/mL. All 10 patients completely recovered. Among reports from other countries of clomipramine hydrochloride overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Manifestations

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Critical manifestations of overdose include cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic toxicity. Other CNS manifestations may include drowsiness, stupor, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, and athetoid and choreiform movements. Cardiac abnormalities may include tachycardia, signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis shock, vomiting, hyperpyrexia, mydriasis, and oliguria or anuria may also be present.

Management

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line, and initiate gastric decontamination. A minimum of 6 hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose: these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of tricyclic overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular: A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation (as needed) should be instituted for patients with dysrhythmias and/or QRS widening. A pH of > 7.60 or a P_{CO2} < 20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase.

Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of clomipramine hydrochloride in 520 adults, and 91 children and adolescents with OCD. During initial titration, clomipramine hydrochloride should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with clomipramine hydrochloride should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, clomipramine hydrochloride should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue clomipramine hydrochloride, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of clomipramine hydrochloride after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED

Clomipramine Hydrochloride Capsules are supplied as follows:

25 mg: Light brown opaque/white opaque capsules, imprinted RUGBY and 5585, in bottles of 100 (NDC 0536-5585-01) and 500 (NDC 0536-5585-05).

50 mg: Light blue opaque/white opaque capsules, imprinted RUGBY and 5586, in bottles of 100 (NDC 0536-5586-01) and 500 (NDC 0536-5586-05).

75 mg: White opaque/white opaque capsules, imprinted RUGBY and 5587, in bottles of 100 (NDC 0536- 5587-01) and 500 (NDC 0536-5587-05).

Do not store above 30°C (86°F). Protect from moisture.

Dispense in a tight container as defined in USP/NF.

Caution: Federal law prohibits dispensing without prescription.

ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with clomipramine hydrochloride. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

Manufactured by
CHELSEA LABORATORIES, INC.
Monroe, NC 28111

Rev. 7/97

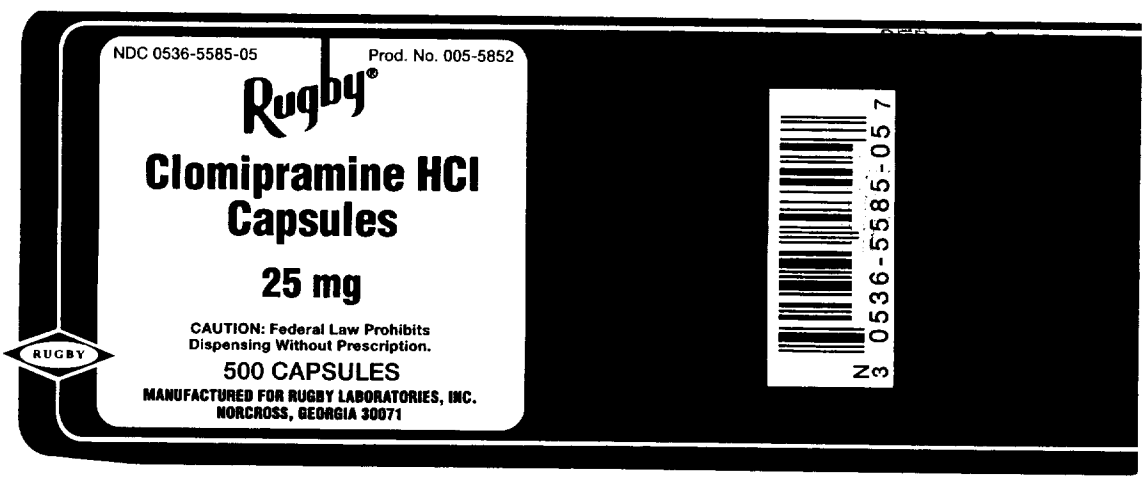
Mango

Clomipramine Hydrochloride Capsules, 25 mg, 50 mg, 75 mg
ANDA 74-751

Final Printed Labels - 25 mg Capsules

100 count

500 count

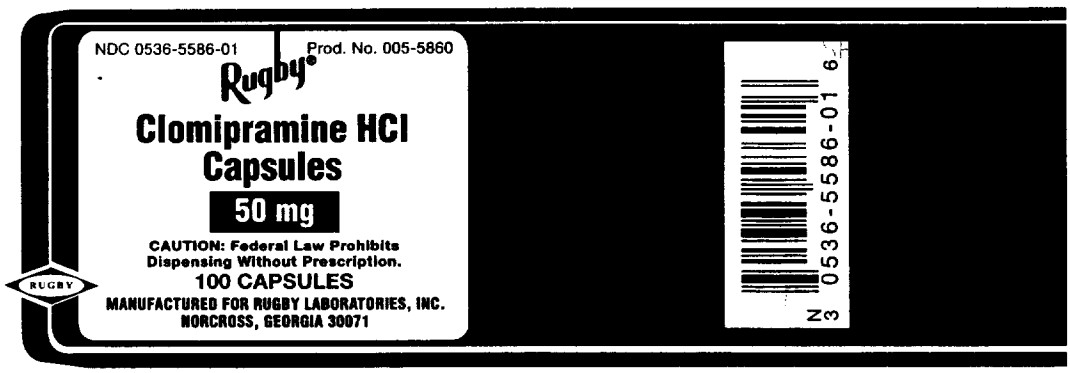


3

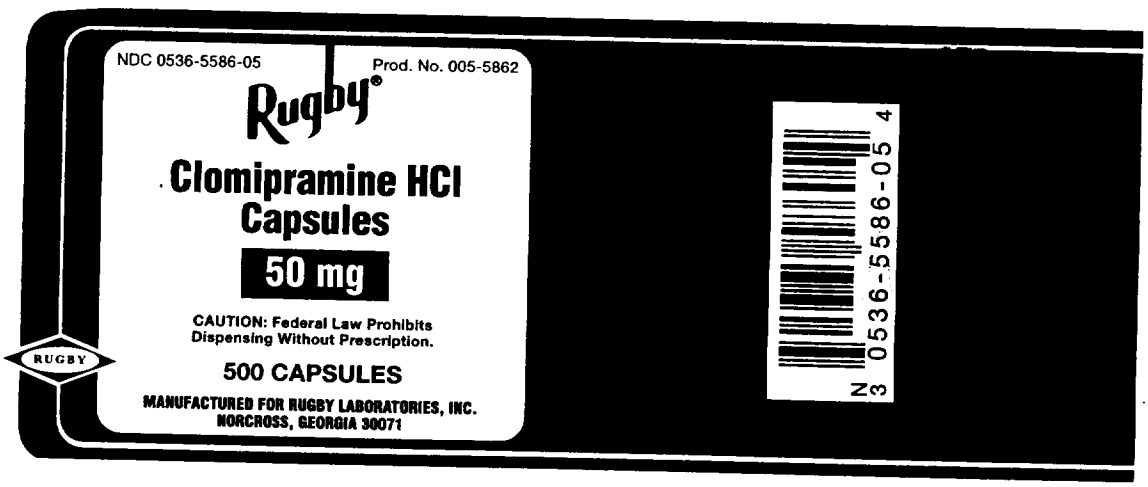
Clomipramine Hydrochloride Capsules, 25 mg, 50 mg, 75 mg
ANDA 74-751

Final Printed Labels - 50 mg Capsules

100 count



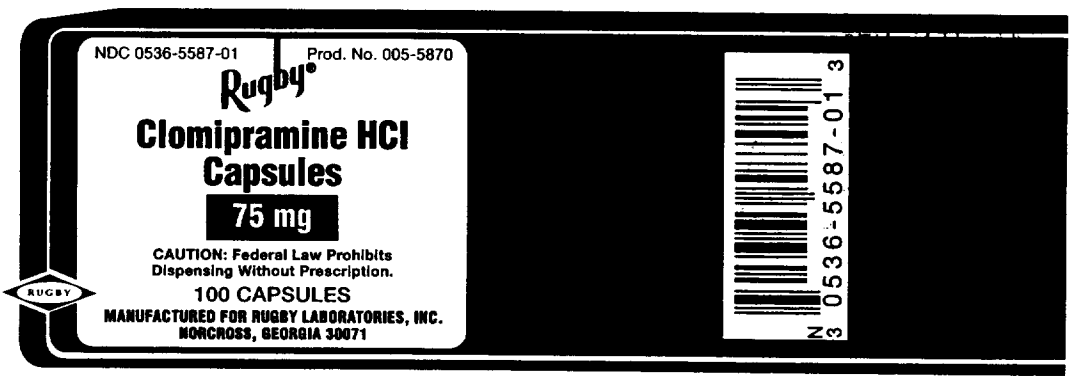
500 count



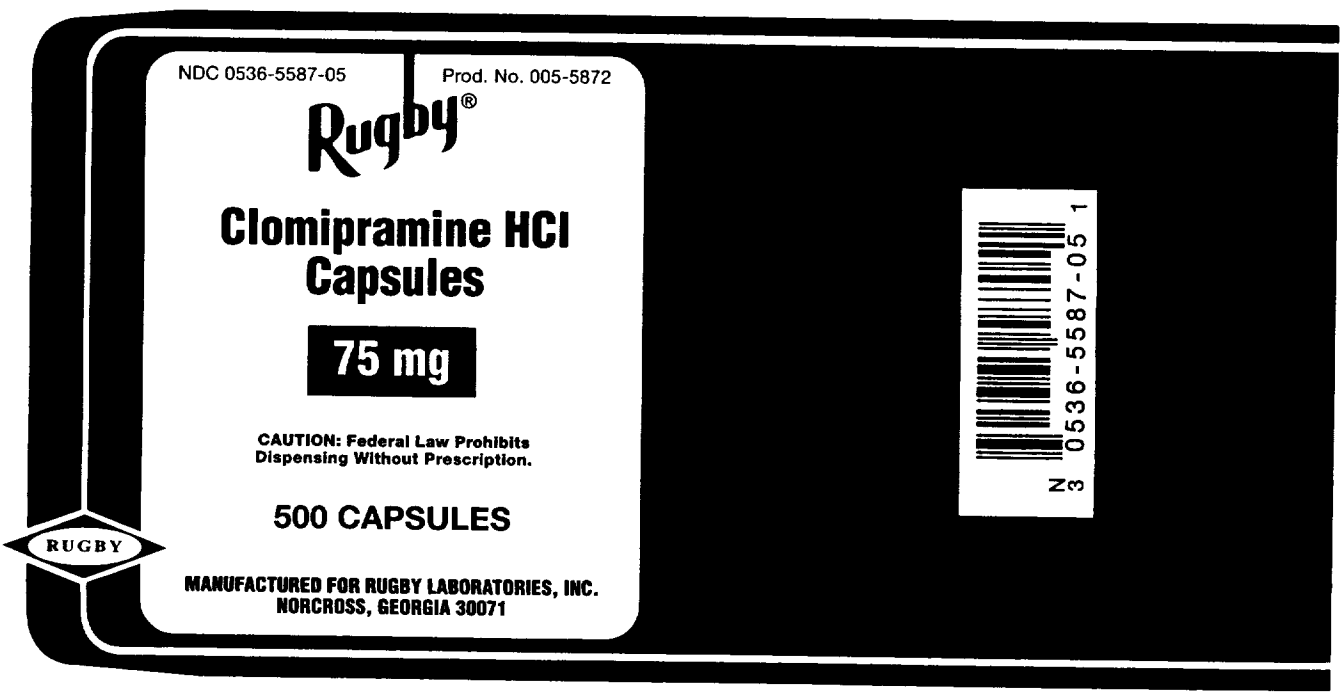
Clomipramine Hydrochloride Capsules, 25 mg, 50 mg, 75 mg
ANDA 74-751

Final Printed Labels - 75 mg Capsules

100 count



500 count



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74751

CHEMISTRY REVIEW(S)

APPROVAL PACKAGE SUMMARY FOR 74-751

ANDA: 74-751

FIRM: Chelsea Laboratories, Inc.

DRUG: Clomipramine Hydrochloride

DOSAGE: Capsules

STRENGTH: 25, 50, and 75 mg

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 8/27/98

BIO STUDY/BIOEQUIVALENCE STATUS: Bio acceptable 7/8/98

METHODS VALIDATION: The methods are satisfactory 9/11/96

STABILITY: the firm has submitted 3 months satisfactory accelerated stability data at 40CC/75%RH and 6 months room temperature at 25-30°C for 25, 50 and 75 mg in 100's and 500's package sizes.

LABELING REVIEW STATUS: Labeling is satisfactory

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has submitted the proposed master formula and manufacturing instructions for the 25, 50 and 75 mg.
The firm has provided the capsule blend executed batch record (2215QS), executed batch record for 25 mg, executed batch record for 50 mg and executed batch record for 75 mg. The firm will be using the same drug substance supplier, equipment and manufacturing process.

COMMENTS: The Application is Approvable.

/S/ 9/28/98

Reviewer: Nashed E. Nashed, Ph.D. Date: 9/16/98

Supervisor: Paul Schwartz, Ph.D. PJ 9/16/98, 9/23/98

X:\NEW\FIRMSAM\CHELSEA\LTRS&REV\74-751.SUM

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 74-751

3. NAME AND ADDRESS OF APPLICANT

Chelsea Laboratories, Inc.
8606 Reading Rd.
Cincinnati, OH 45215

4. LEGAL BASIS FOR SUBMISSION

The firm has indicated that to the best of their knowledge, no pending patents exist for clomipramine hydrochloride. Also, no pending exclusivities exist for clomipramine hydrochloride.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Clomipramine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original 9/19/95
Amendment 12/17/96
Amendment 12/19/97
Amendment 8/10/98
Amendment 9/10/98

10. PHARMACOLOGICAL CATEGORY

Treatment of obsessions and compulsions in patients with obsessive-compulsive disorder.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's

13. DOSAGE FORM

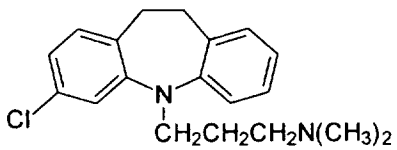
Capsules

14. POTENCY

25, 50, and 75 mg

15. CHEMICAL NAME AND STRUCTURE

Clomipramine Hydrochloride. $C_{19}H_{23}ClN_2$•HCl. 351.3. 5*H* -Dibenz[*b,f*]azepine-5-propanamine, 3-chloro-10,11-dihydro-*N* ,*N* -dimethyl-, monohydrochloride. 17321-77-6. USAN 1993, page 159.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 9/16/98

Supervisor: Paul Schwartz, Ph.D. 9/17/98

cc: ANDA 74-751
Division File
Field Copy

Endorsements:
HFD-627/N.Nashed, Ph.D./9-16-98 9/23/98
HFD-627/P.Schwartz, Ph.D./9-17-98 9/22/98
X:\NEW\FIRMSAM\CHELSEA\LTRS&REV\74-751.2
F/T by: bc/9-22-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74751

BIOEQUIVALENCY REVIEW(S)

MAR 7 1996

Clomipramine Hydrochloride
Capsules, 25 mg, 50 mg and 75 mg
ANDA #74-751
Reviewer: Sikta Pradhan
WP #74751SDW.995

Chelsea Lab., Inc.
Cincinnati, Ohio
Submission Date:
September 19, 1995

REVIEW OF BIOEQUIVALENCE STUDIES AND WAIVER REQUESTS

Introduction:

Clomipramine hydrochloride is a tricyclic antidepressant. It is used as an anti-obsessional agent. The pharmacologic action is thought to be through its effect on serotonergic neural transmission. Clomipramine hydrochloride is white to off-white crystalline powder, soluble in water, methanol and in methylene chloride, and insoluble in ethyl ether and in hexane. It is rapidly and completely absorbed after oral administration and undergoes extensive first pass N-demethylation to the major metabolite, monodesmethylclomipramine. Following a single oral 50 mg dose, peak plasma concentrations of clomipramine from 56 to 154 ng/ml are observed after 2 to 6 hours. After a 150 mg dose, the half-life of Clomipramine ranges from 19 hours to 37 hours and that of monodesmethylclomipramine ranges from 54 hours to 77 hours. Food does not appear to affect the systemic bioavailability of clomipramine hydrochloride capsules. The innovator labeling indicates that in multiple dose studies, the steady-state plasma concentrations (C_{ss}) and area-under-plasma-concentration-time curve (AUC) of Clomipramine and desmethylclomipramine were not proportional to the dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_{ss} and AUC are approximately linearly related to dose between 100-150 mg/day.

A dose of 25 mg/day is recommended as an initial dose administered with food. The dose should be increased gradually to approximately 100 mg during the first 2 weeks. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

The drug is currently marketed by Basel Pharmaceuticals, Inc. as Anafranil^{R} 25 mg, 50 mg and 75 mg capsules.

Objective:

The purpose of this single dose, two-way crossover study is to determine the bioequivalence of the test 25 mg Clomipramine capsule relative to the reference 25 mg Anafranil^{R} capsule marketed by Basel Pharmaceuticals, Inc. in healthy male

volunteers under fasted condition.

In-Vivo Study:

The study was conducted at
under the direction of
(Principal Investigator). Clinical and analytical studies were conducted under the supervision of
(Clinical Study Manager) and
(Analytical Project Manager), respectively.

Study Design:

A randomized, two-way crossover single dose study (Protocol No.920438; Proj. No.920438/DFJ) was conducted using thirty-six (36) healthy volunteers under fasting condition.

Subjects:

Thirty six (36) male volunteers between 18-43 years (see attachment #1 for demographics) of age and within ± 15% of their ideal body weight according to Metropolitan Life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Test (hematology, blood chemistry, urinalysis, etc.). The subjects were restricted from any other medications including OTC drugs for at least seven days prior to the first drug administration until after the study was completed. The volunteers were not allowed to drink alcoholic beverages, caffeine or xanthine-containing food for 24 hours before dosing and throughout the period of sample collection.

Clinical Study Dates: Period I: February 14, 1995
Period II: March 7, 1995

Treatments:

A. 25 mg X 1 Clomipramine HCl Capsule (Chelsea), Lot #2216 SQ, Lot size not given, Potency of the capsule, 98.0%

B. 25 mg X 1 Anafranil^{R} Capsule (Basel Pharm), Lot #1T165404, Potency of the capsule, 96.1%, Exp. Date: April 1997

Dose Administration:

A single dose of 25 mg Clomipramine hydrochloride was orally administered with 240 ml of water after an overnight fast. Subjects were dosed while seated in bed and remained seated in bed for the first 4 hours after drug administration in order to minimize possible drug-induced hypotension. A mouth check to assure drug ingestion has not been mentioned in the study protocol.

Meal and Fluid Intake:

All volunteers fasted for 4 hours after drug administration. Subjects were required to drink 240 mL of water 1 hour before dosing. Water intake was then restricted until one hour after drug administration (not including the water administered with the dose) but was allowed at all other times. Standard non-fat meals was served. No caffeine or xanthine containing food or beverages was permitted. During housing, meal plans were identical for both periods.

Blood Sample Collection:

Blood samples (2x10 mL) were collected in vacutainer containing EDTA before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 144, 192 and 240 hours (1x10 mL) after dosing. The blood samples were processed and the plasma samples were delivered under frozen conditions to the analytical facility for the analysis of clomipramine and monodesmethylclomipramine in plasma samples. Samples were stored at nominal temperature of $-22^{0}C$ until analyzed.

Housing:

Subjects were housed from 12 hours before dosing until after the 48-hour blood draw in each period and they returned for the draws at 72, 96, 144, 192 and 240 hours after dosing.

Drug Washout Period: Twenty-one (21) days between doses

Safety Monitoring:

To monitor safety, sitting blood pressure and heart rate were measured before dosing and at approximately 2 and 4 hours after dosing. No safety problems were encountered.

Assay Methodology:

Absolute Recovery Data:
CMI: 84.6 - 87.9% at concentrations ng/mL
DMI: 74.7 - 77.6% at concentrations ng/mL
Imipramine (IS for CMI): 89.4% at conc. 4.00 mcg/mL
Desipramine (IS for DMI): 87.4% at conc. 0.80 mcg/mL
Conditions: Has not been given

Date(s) of Preparation of QC Samples: February 28, 1995
April 10, 1995
April 13, 1995
April 27, 1995

Specificity: No interference was observed at the retention times of either CMI, DMI or internal standards. However, the firm is required to provide the retention time of each of them mentioned above.

Linearity: The standard plots for both CMI and DMI were linear in the concentration range of ng/mL for CMI and ng/mL for DMI with the correlation coefficient of 0.9997 and 0.9995, respectively.

Sensitivity: The lower limit of quantitation (LLOQ) for both CMI and DMI was 0.50 ng/mL; any value less than this was reported as zero.

Precision:

A. **Pre-study validation:**

For CMI:
Intraday Precision from Standards:
3.3% (CV) at 0.5 ng/mL
6.3% (CV) at 1.0 ng/mL
4.4% (CV) at 9.99 ng/mL
2.3% (CV) at 29.97 ng/mL
1.3% (CV) at 49.95 ng/mL
2.7% (CV) at 69.93 ng/mL
2.6% (CV) at 89.91 ng/mL
1.4% (CV) at 99.90 ng/mL

Intraday Precision and Accuracy Observed from QC Controls:
6.5% (CV) at 0.50 ng/mL; Accuracy (%): 109.6
12.6% (CV) at 1.50 ng/mL; Accuracy (%): 80.5
5.3% (CV) at 40.03 ng/mL; Accuracy (%): 99.7
7.1% (CV) at 80.06 ng/mL; Accuracy (%): 90.6

Interday Precision from QC Controls:
9.3% (CV) at 0.5 ng/mL Accuracy (%): 102
14.7% (CV) at 1.5 ng/mL Accuracy (%): 92.2
7.6% (CV) at 40.3 ng/mL Accuracy (%): 98.9
5.1% (CV) at 80.06 ng/mL Accuracy (%): 94.3

For DMI:
Intraday Precision from Standards:
4.2% (CV) at 0.5 ng/mL
4.5% (CV) at 1.01 ng/mL
4.4% (CV) at 4.02 ng/mL
6.5% (CV) at 6.04 ng/mL
7.7% (CV) at 10.06 ng/mL
3.1% (CV) at 15.09 ng/mL
3.9% (CV) at 18.11 ng/mL
3.0% (CV) at 20.12 ng/mL

Intraday Precision and Accuracy Observed from QC Controls:
3.4% (CV) at 0.5 ng/mL; Accuracy (%): 106
10.2% (CV) at 1.5 ng/mL; Accuracy (%): 85.1
4.4% (CV) at 8.0 ng/mL; Accuracy (%): 93.8
7.3% (CV) at 17.01 ng/mL; Accuracy (%): 90.1

Interday Precision from QC Controls:
10.9% (CV) at 0.5 ng/mL Accuracy (%): 110.5
12.6% (CV) at 1.5 ng/mL Accuracy (%): 95.6
10.1% (CV) at 8.0 ng/mL Accuracy (%): 96.6
6.3% (CV) at 17.01 ng/mL Accuracy (%): 94.3

B. **Within-study validation:**

For CMI:
Interday Precision and Accuracy Observed from Standards:
10.5% (CV) at 0.5 ng/mL; Accuracy: 104.8%
11.7% (CV) at 1.0 ng/mL; Accuracy: 98.3%
11.4% (CV) at 9.99 ng/mL; Accuracy: 97.6%
6.7% (CV) at 29.97 ng/mL; Accuracy: 98.8%
5.3% (CV) at 49.95 ng/mL; Accuracy: 101.3%
3.9% (CV) at 99.90 ng/mL; Accuracy: 99.4%

Interday Precision and Accuracy Observed from Control Samples:
15.5% (CV) at 1.5 ng/mL; Accuracy: 97.9%
7.4% (CV) at 40.03 ng/mL; Accuracy: 100.4%
6.7% (CV) at 80.06 ng/mL; Accuracy: 97.4%

For DMI:
Interday Precision and Accuracy Observed from Standards:
11.2% (CV) at 0.5 ng/mL; Accuracy: 106.3%
7.1% (CV) at 1.01 ng/mL; Accuracy: 97.9%
8.4% (CV) at 4.02 ng/mL; Accuracy: 97.2%
6.5% (CV) at 6.04 ng/mL; Accuracy: 97.6%
4.5% (CV) at 15.09 ng/mL; Accuracy: 99.8%
5.1% (CV) at 20.12 ng/mL; Accuracy: 100.8%

Interday Precision and Accuracy Observed from Control Samples:
7.7% (CV) at 1.5 ng/mL; Accuracy: 96.0%
5.8% (CV) at 8.0 ng/mL; Accuracy: 97.5%
5.7% (CV) at 17.01 ng/mL; Accuracy: 96.8%

Stability:

1. Control samples of CMI (at conc. ng/mL) were found to be stable for 34 hours in autosampler at 20°C. Control samples of DMI (at conc. ng/mL) were found to be stable for 34 hours in autosampler at 20°C.

2. CMI frozen control samples (at conc. ng/mL) were found to be stable through three freeze/thaw cycles. DMI frozen control samples (at conc. ng/mL) were found to be stable through three freeze/thaw cycles.

3. Stock solution of CMI in methanol is stable for 256 days at -22°C ± 10°C.

4. Stock solution of DMI in methanol is stable for 256 days at -22°C ± 10°C.

5. Long term freezer stability for both CMI & DMI in human plasma is 178 days at -22°C.

Results:

Thirty six (36) male volunteers were selected for the study. Two subjects (subject #5 subject #13) did not complete the study due to personal reasons. Thus a total of 34 subjects completed the study, of which one subject (No.25) vomited within 24 hours of drug administration. But no incidence of diarrhea was reported.

The firm has stated that the concentration values for Subject No. 34 could not be reported (no reason was provided) for CMI, and was eliminated from the statistical analysis. Therefore, the statistical analysis was performed on data obtained from 33 subjects (including Subject #25).

Subject #1 completed only Period 1 study. He had no concentration values for CMI and DMI in Period 2. This subject reported that he had retched 12 minutes after dosing.

As per protocol, statistical analyses were also performed on data excluding subjects who had vomited within 24 hours of dosing (N=32).

There were a number of blood collections that deviated from the target times (see attachment #2). The actual blood collection time was used for the calculation of the value for the pharmacokinetic parameters. Several adverse events were reported in twenty-four hours of thirty-six subjects dosed. However, there were no serious adverse events or any events which required terminating any subjects from the study. Mean plasma CMI and DMI levels of 33 subjects are presented in Table 1 and Table 2,

respectively, below. The plasma profile of CMI is presented in Figure 1 (attached).

Table 1
Mean Plasma Clomipramine Levels (ng/mL)
(N=33)

Time (hour)	Test (A) 1X25mg Cap (Chelsea) Lot #2216 SQ	Reference (B) 1X25mg Anafranil® Cap (Basel) Lot #1T165404
0	0	0
0.5	0.026 (574*)	0.14 (325)
1.0	0.86 (122)	0.67 (120)
1.5	3.23 (78)	2.95 (86)
2.0	5.26 (52)	5.34 (67)
2.5	6.92 (48)	7.57 (65)
3.0	7.84 (44)	9.28 (59)
3.5	8.96 (36)	9.29 (55)
4.0	9.11 (36)	10.16 (52)
5.0	8.81 (37)	9.90 (46)
6.0	8.64 (35)	9.42 (57)
8.0	6.87 (36)	7.17 (51)
12.0	4.54 (35)	4.34 (52)
24.0	2.16 (42)	2.34 (49)
36.0	1.17 (44)	1.28 (56)
48.0	0.82 (57)	0.86 (71)
72.0	0.31 (138)	0.41 (108)
96.0	0.11 (243)	0.16 (211)
144.0	0.02 (574)	0.02 (566)
192.0	0.00	0.01 (574)
240.0	0.00	0.02 (574)

* Coefficient of Variation
N = Total Number of subjects (including subject #25 who vomited) completed the study.

Table 2
Mean Plasma Monodesmethylclomipramine Levels (ng/mL)
(N=33)

Time (hour)	Test (A)	Reference (B)
0	0.02 (583*)	0.02 (583)
0.5	0.02 (583)	0.02 (583)
1.0	0.06 (329)	0.05 (327)
1.5	0.43 (113)	0.26 (164)
2.0	0.85 (72)	0.75 (76)
2.5	1.35 (62)	1.25 (52)
3.0	1.71 (55)	1.79 (41)
3.5	1.86 (51)	1.89 (42)
4.0	2.19 (41)	2.18 (44)
5.0	2.59 (41)	2.65 (43)
6.0	2.94 (44)	2.90 (43)
8.0	2.95 (45)	3.01 (47)
12.0	2.85 (47)	2.74 (47)
24.0	2.24 (63)	2.32 (59)
36.0	1.93 (76)	2.01 (80)
48.0	1.70 (87)	1.74 (90)
72.0	1.28 (110)	1.32 (111)
96.0	0.93 (139)	0.90 (155)
144.0	0.43 (237)	0.50 (218)
192.0	0.33 (272)	0.32 (254)
240.0	0.23 (276)	0.24 (280)

The pharmacokinetic parameters for Clomipramine derived from 33 subjects' plasma data are presented in Table 3 and Table 4, respectively, below:

Table 3

Mean Pharmacokinetic Parameters for Clomipramine in Plasma

Parameters (Arithmetic Means)	Test(A) (Subj=N=33)	Ref.(B) (Subj=N=33)	100xA/B
AUC_{0-T} (ng.hr/mL)	159.27 (41*)	171.52 (58)	93
AUC_{0-inf} (ng.hr/mL)	188.56 (41) (N=32)	198.75 (47) (N=30)	95
C_{MAX} (ng/mL)	10.40 (35)	11.31 (52)	92
T_{max} (hour)	4.23 (26)	4.45 (25) (N=32)	
t1/2 (hour) —	24.16 (91) (N=32)	23.56 (68) (N=30)	
KE (1/hour)	0.043 (47) (N=32)	-0.039 (45) (N=30)	

Parameters (Using LSM)	Test(A)	Ref.(B)	100xA/B	90% C.I.
$LnAUC_{0-T}$	4.9809	5.0274		**84; 108**
Geometric mean	145.60	152.54	95	
$LnAUC_{0-inf}$	5.1202	5.1737		**84; 107**
Geometric mean	167.37	176.57	95	
LnC_{MAX}	2.2694	2.3483		**82; 104**
Geometric mean	9.67	10.47	92	

* Coefficient of Variation
LSM - Least Squares Means

Both test and reference drugs produced peak concentration for CMI between 3 to 6 hours after their administration in 33 subjects (including the subject #25 who had vomited within 24 hours after dosing). There was almost no difference between the test and reference products in AUC_{0-T}, AUC_{0-inf} and C_{MAX} values. The 90% confidence intervals for $LnAUC_{0-T}$, $LnAUC_{0-inf}$ and LnC_{MAX} of the test product remained within the acceptable range of 80 - 125%.

Since the values for AUC_{0-t} and C_{MAX} of Subject #1 were zero for Period II, $LnAUC_{0-t}$ and LnC_{MAX} could not be used in the analysis. The firm included the Period I data from Subject #1 in the analysis. However, the ESTIMATE and the STANDARD ERROR OF ESTIMATE should have been the same as if no data from Subject #1 had been used.

Mean pharmacokinetic parameters derived from plasma data of 32 subjects (excluding data of subject #25) also meet the acceptable criteria, and the 90% confidence intervals for $LnAUC_{0-T}$, $LnAUC_{0-inf}$ and LnC_{MAX} of the test product remained within the acceptable range of 80 - 125%.

DMI levels of the test and reference products are comparable. However, in some subjects, the carryover effect was observed in Period II. The firm did not performed statistical analysis on DMI data and therefore, did not fulfill the Agency drug approval requirements.

II. Limited food study:

The firm has submitted the results of a single oral 25 mg dose three-way crossover post-prandial bioequivalence study conducted on the test product, 25 mg Clomipramine and the reference product, 25 mg Anafranil^{R} (Basel) in order to determine the effect of food on the bioavailability of those products according to the protocol #940494.

Dosing Schedule:

Eighteen (18) healthy male volunteers entered into the study after completing a physical examination and laboratory screening tests. Subjects No.1-18 were dosed on the following dates:

Period I February 22, 1995
Period II March 15, 1995
Period III April 5, 1995

As all eighteen subjects could not finish the study, 6 additional subjects were also dosed after medical examinations. Subjects No.19-24 were dosed on the following dates:

Period I April 21, 1995
Period II May 12, 1995
Period III June 2, 1995

Treatment A: 1x25 mg Clomipramine capsule (Chelsea), lot #2216SQ after an overnight fast

Treatment B: 1x25 mg Clomipramine capsule (Chelsea), lot #2216SQ, 30 minutes after a standard breakfast

Treatment C: 1x25 mg Clomipramine capsule (Basel^{R}), lot #1T165404, 30 minutes after a standard breakfast

Drug Washout Period: 21 days

Blood Sample Collection:

Ten (10) mL blood samples were collected by venipuncture into Vacutainer tubes containing EDTA at 0 (predose) and at 0.5, 1.0, 1.5, 2, 2.5 3, 3.5 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 144, 192 and 240 hours after dosing. The plasma samples processed and kept frozen at -22^{0}C till analysis.

Of the 18 volunteers originally enrolled, 5 subjects did not complete the study. Subject Nos 4 and #17 were withdrawn from the study due to a medical event. Subject Nos. 7, 9 and 18 elected to withdraw from the study due to personal reasons. Subject No. 14 was withdrawn from the study prior to dosing in Period III due to medical events requiring medication. As per protocol, a decision was taken before the commencement of sample analysis to enroll six (6) additional subjects to replace those subjects who withdrew from the study. Of these, two subjects did not complete the study. Subject Nos. 20 and 21 elected to withdraw from the study due to personal reasons. Subject No. 24 was withdrawn from the study prior to dosing in Period III due to medical events requiring medication.

The firm was not able to report the clomipramine level of all periods of subject #3 due to analytical problems, and therefore, this subject's data was excluded from statistical and pharmacokinetic analysis. However, the plasma data (Period I and Period II) of subjects #14 and #24 were included in data analysis.

As per protocol, statistical analyses for clomipramine was performed on two different data sets:

1) The data set excluding data from Subject Nos. 22 and 23 who had vomited in Period I, N=14 (including Subject Nos. 14 and 24, who completed Phase I and Phase II but not Phase III).
2) All available data (including Subject Nos. 22 and 23), N=16.

Mean plasma clomipramine levels and the pharmacokinetic parameters of 16 subjects are presented in Tables 4 and 5, respectively. The plasma profile of CMI is presented in Figure 2 (attached).

Table 4
Mean Plasma Clomipramine Levels (ng/mL)

Time (hour)	TEST (A) **Fasted** *Mean (CV) N=16	TEST (B) **Fed** *Mean (CV) N=16	Reference (C) **Fed** *Mean (CV) N=15
0 Pre-dose	0	0	0
0.5	0 (00); N=15	0 (00)	0 (00)
1.0	1.54 (97)	0.27 (160)	0.39 (174)
1.5	4.70 (90)	1.49 (107)	1.68 (181)
2	8.23 (61); N=15	3.37 (93)	3.42 (132)
2.5	10.46 (45); N=15	5.04 (77)	5.09 (85)
3	10.97 (37)	8.16 (62)	7.55 (61)
3.5	10.98 (37); N=15	8.97 (57)	8.29 (50)
4	11.31 (34)	10.44 (57)	10.35 (41)
5	11.15 (33)	10.80 (48)	11.90 (25)
6	10.23 (34);	10.40 (45)	11.41 (15)
8	7.85 (45); N=15	9.26 (41)	10.81 (22)
12	5.42 (35)	6.02 (44)	7.26 (26)
24	2.69 (38)	2.89 (41)	3.77 (29)
36	1.57 (41)	1.77 (53)	1.99 (34)
48	1.19 (47)	1.21 (56)	1.40 (38)
72	0.45 (101)	0.49 (114)	0.59 (81)
96	0.16 (186)	0.18 (186)	0.24 (154)
144	0 (00)	0.03 (400)	0.03 (387)
192	0 (00); N=15	0 (00)	0 (00)
240	0 (00); N=15	0 (00)	0 (00)

Total Number of Subjects = N
* Arithmetic Means

Table 5
Mean Pharmacokinetic Parameters of Clomipramine

Parameters (arithmetic means)	Test(A) Fasted (N=16)	Test(B) Fed	REF.(C) Fed	(B/C)	(B/A)
AUC_{0-T} (ng.hr/mL)	201.0 (41)* (N=15)	210.9 (51) (N=16)	247.6 (26) (N=15)	1.03	0.70
AUC_{0-inf} (ng.hr/mL)	230.3 (41) (N=13)	246.6 (42) (N=15)	271.3 (26) (N=15)	1.02	0.71
C_{MAX} (ng/mL)	13.0 (32) (N=15)	12.1 (46) (N=16)	13.38 (17) (N=15)	1.10	0.58
T_{max} (hour)	3.83 (27) (N=15)	5.09 (25) (N=16)	5.27 (27) (N=15)		
t1/2 (hour)	21.84(36) (N=13)	21.9 (44) (N=15)	21.83 (38) (N=15)		
KE (1/hour)	0.036(38) (N=13)	0.037(37) (N=15)	0.036 (38) (N=15)		

Log-Transformed data using LSM

Parameters	Test(B) Fed	Ref.(C) Fed	Test Mean (geometric)	Ref. Mean (geometric)	Test/Ref.(%)
$LAUC_{0-T}$	5.16660405	5.48438787	175.32	240.90	72.8
$LAUC_{0-inf}$	5.44847885	5.54411286	232.40	255.73	90.1
LC_{MAX}	2.35702702	2.55922172	10.56	12.92	81.7

* Coefficient of Variation
Total Number of Subjects = N
Subject Nos. 22 & 23 (who vomited within 24 hours of drug administration) were included in data analysis.

Table 6
Mean Pharmacokinetic Parameters of Clomipramine

Parameters (arithmetic means)	Test(A) Fasted (N=14)	Test(B) Fed	REF.(C) Fed	(B/C)	(B/A)
AUC_{0-T} (ng.hr/mL)	187.5 (40)* (N=13)	209.1 (40) (N=14)	232.2 (23) (N=13)	0.90	1.11
AUC_{0-inf} (ng.hr/mL)	212.3 (40) (N=11)	231.5 (38) (N=14)	255.4 (23) (N=13)	0.91	1.09
C_{MAX} (ng/mL)	12.71 (34) (N=13)	12.26 (38) (N=14)	13.15 (17) (N=13)	0.93	0.96
T_{max} (hour) (N=13)	3.64 (27) (N=13)	5.11 (26) (N=14)	5.23 (29) (N=13)		
t1/2 (hour)	19.96(32) (N=11)	20.63(41) (N=14)	20.04(35) (N=13)		
KE (1/hour)	0.038(34) (N=11)	0.038(34) (N=14)	0.039(35) (N=13)		

Log-Transformed data using LSM

Parameters	Test(B) Fed	Ref.(C) Fed	Test Mean (geometric)	Ref. Mean (geometric)	Test/Ref.(%)
$LAUC_{0-T}$	5.261289	5.397548	192.73	220.86	87
$LAUC_{0-inf}$	5.373947	5.494433	215.71	243.33	89
LC_{MAX}	2.457444	2.510222	11.67	12.30	95

Subject Nos. 22 & 23 were withdrawn from statistical analysis.

From these results, it appears that food does not affect the systemic bioavailability of clomipramine. Mean differences (both arithmetic and least squares means of 14 subjects, excluding subjects #22 and #23 who vomited) in AUC_{0-T}, AUC_{0-inf} and C_{MAX} of the test and reference products dosed under fed conditions are within the 20% range.

Formulations:

The compositions of Clomipramine 25.0 mg, 50.0 mg and 75.0 mg Capsules are presented below:

Ingredients	**Strengths (mg/ capsule)**		
	25.0 mg Cap*	**50.0 mg Cap****	**75.0 mg Cap*****
Clomipramine HCl BP	25.0	50.0	75.0
Pregelatinized Starch, NF (Starch 1500)			
Pregelatinized Starch, NF (Starch 1500)			
Colloidal Silicon Dioxide, NF (Cab-O-Sil)			
Magnesium Stearate, NF			
Total Weight			

* Description: #4 Lt. Brown Op/White Op Hard Gelatin Capsule Imprinted RUGBY 5585, filled with white powder.

** Description: #2 Lt. Blue Op/White Op Hard Gelatin Capsule Imprinted RUGBY 5586, filled with white powder.

*** Description: #1 Lt. White Op/White Op Hard Gelatin Capsule Imprinted RUGBY 5587, filled with white powder.

In-Vitro Dissolution:

The firm has conducted the dissolution testing on Clomipramine Capsules, 25 mg, 50 mg and 75 mg using the following dissolution condition:

Apparatus:	USP XXIII Basket I
Speed:	RPM 100
Medium:	900 mL 0.1N HCl at 37°C
Tolerances:	% (Q) in 30 minutes

This dissolution testing condition is not acceptable to the Agency, and therefore, the dissolution data submitted to us will not be reviewed.

Recommendations:

1. The in vivo Bioequivalence studies conducted (under fed and fasted conditions) by Chelsea Laboratories, Inc. on its 25 mg Clomipramine Hydrochloride Capsules, Lot # 2216 SQ versus the listed reference product, Anafranil[R] Capsule, 25 mg, manufactured by Basel Pharmaceuticals has been found to be incomplete by the Division of Bioequivalence for the reasons stated in Comments #2 - 7 above.

2. The waiver of in vivo bioequivalence study on Clomipramine Hydrochloride 50 mg and 75 mg Capsules has been denied. The firm should resubmit the waiver request for its test product with its response to the deficiencies above.

/S/

Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ 3/7/96

cc: ANDA # 74751SDW.995 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Pradhan), Drug File, Division File.

SP/02-21-96/X:\wpfile\Pradhan\74751SDW.995

Figure 1

Project No. 920438

Mean Plasma Clomipramine Concentrations

(Linear Plot)

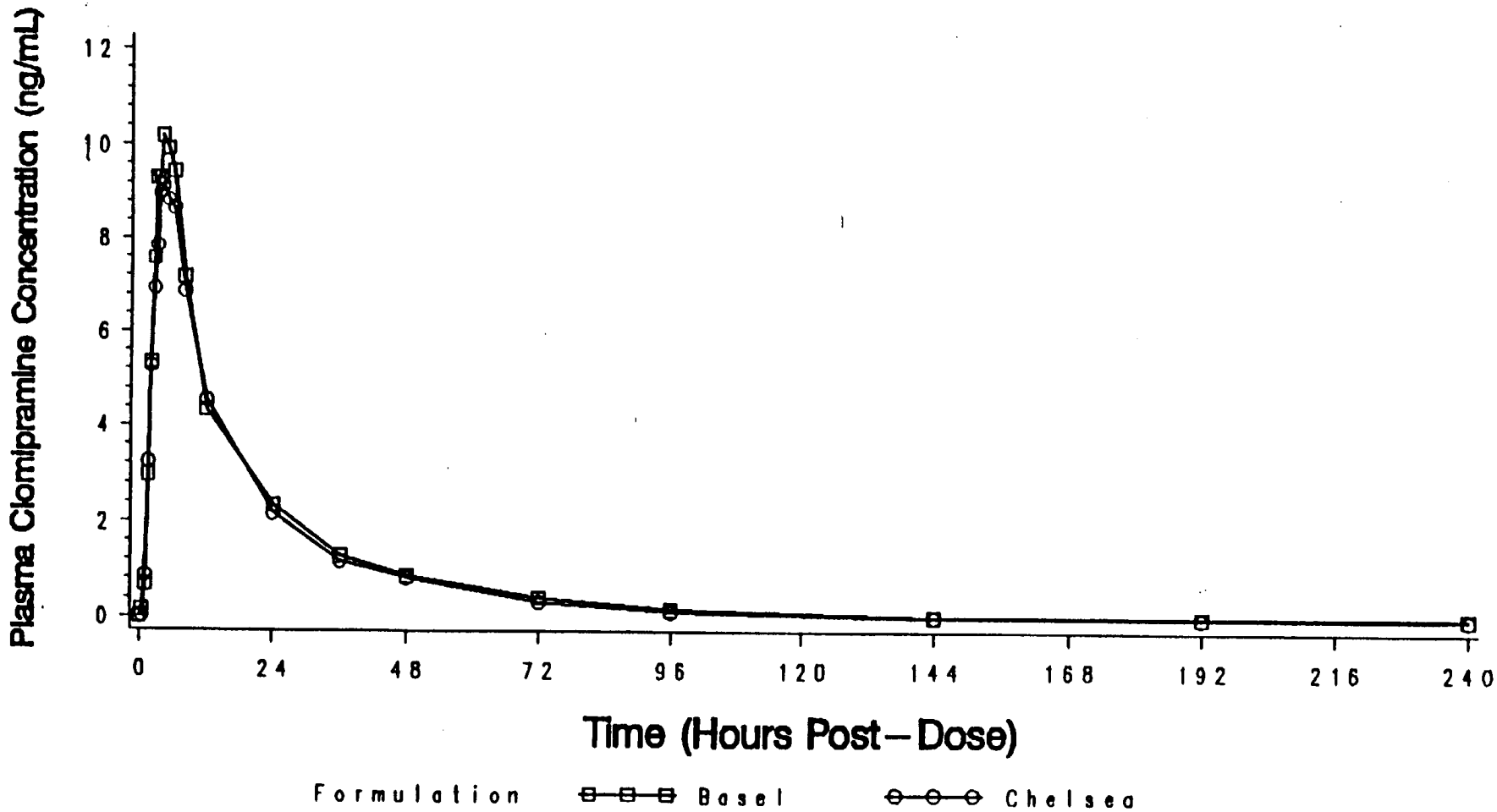
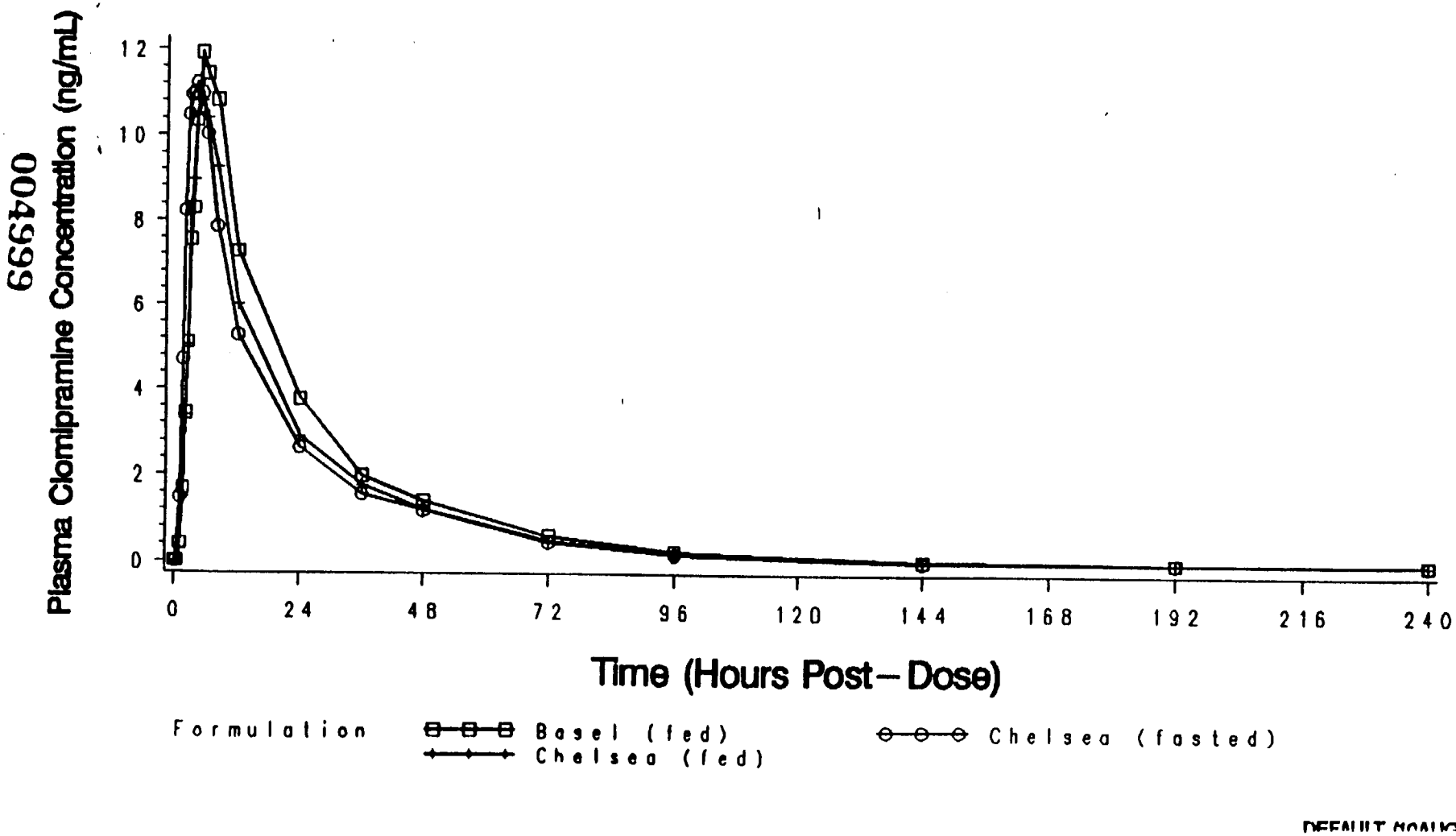


Figure 2

Project No. 940494

Mean Plasma Clomipramine Concentrations

(Linear Plot)



Attachment #1

SUBJECT DEMOGRAPHICS AND RANDOMIZATION SCHEME

	Subject	Product Code Period 1 2	Age (yrs)	Height (cm)	Weight (kg)	Frame	Race	Gender
	1	A B	30	177	64.8	Medium	Caucasian	Male
	2	B A	26	171	64.1	Medium	Caucasian	Male
	3	B A	37	171	76.8	Medium	Caucasian	Male
	4	B A	40	174	78.8	Medium	Caucasian	Male
*	5	A B	25	178	72.4	Medium	Caucasian	Male
	6	A B	35	170	66.6	Small	Caucasian	Male
	7	A B	37	172	80.9	Medium	Caucasian	Male
	8	B A	39	174	82.7	Medium	Caucasian	Male
	9	A B	41	176	75.3	Medium	Caucasian	Male
	10	B A	22	176	72.5	Medium	Caucasian	Male
	11	A B	42	185	74.2	Medium	Caucasian	Male
	12	A B	38	174	64.0	Medium	Caucasian	Male
*	13	A B	21	175	62.2	Small	Caucasian	Male
	14	B A	27	178	77.3	Small	Caucasian	Male
	15	B A	18	177	69.0	Medium	Caucasian	Male
	16	B A	41	183	74.1	Medium	Caucasian	Male
	17	B A	38	177	91.3	Large	Caucasian	Male
	18	A B	20	179	64.6	Medium	Caucasian	Male
	19	A B	37	172	63.0	Small	Caucasian	Male
	20	A B	19	170	61.1	Small	Caucasian	Male
	21	A B	37	168	67.2	Small	Caucasian	Male
	22	B A	23	170	72.8	Small	Caucasian	Male
	23	B A	23	168	60.0	Medium	Caucasian	Male
	24	B A	20	182	72.0	Medium	Caucasian	Male
	25	A B	18	180	67.0	Medium	Caucasian	Male
	26	B A	20	177	69.4	Small	Caucasian	Male
	27	A B	20	171	64.7	Medium	Caucasian	Male
	28	A B	33	183	87.3	Medium	Caucasian	Male
	29	A B	30	182	85.5	Medium	Caucasian	Male
	30	B A	43	172	67.4	Medium	Caucasian	Male
	31	B A	34	170	75.8	Medium	Caucasian	Male
	32	A B	23	183	82.3	Medium	Caucasian	Male
	33	B A	29	182	77.3	Medium	Caucasian	Male
	34	A B	20	174	71.1	Medium	Caucasian	Male
	35	B A	30	175	79.0	Medium	Caucasian	Male
	36	B A	19	170	61.8	Small	Caucasian	Male
		Mean	29.3	175.4	72.12			
		± SD	8.39	4.81	8.006			
		N	36	36	36			
		CV%	28.6	2.7	11.1			

A = Chelsea 25 mg clomipramine HCl capsules
B = Basel (Anafranil) 25 mg clomipramine HCl capsules

* Subjects did not complete the crossover.

Subject ages are calculated as of Period 1 dosing.

File DEMO.OUT created 31/MAY/95 02:59pm by JACKIES. DataBase Ver# 4.53, Internal Ver# 94.01-F04-R03

Attachment # 2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Comment
A	1	1	72	0	0	58	Late
A	1	1	144	0	0	4	Late
A	2	2	96	0	0	17	Late
A	2	2	144	0	0	12	Late
A	2	2	192	0	0	9	Late
A	5	1	72	0	0	7	Late
A	5	1	144	0	0	10	Late
A	5	1	192				Did not show for blood draw
A	5	1	240				Did not show for blood draw
A	6	1	72	0	0	6	Late
A	9	1	72	0	0	29	Late
A	9	1	96	0	0	41	Late
A	9	1	144	0	0	6	Late
A	9	1	240	0	0	29	Late
A	10	2	96	0	1	5	Late
A	12	1	2	0	0	3	Late
A	12	1	72	0	0	11	Late
A	13	1	96	0	0	3	Late
A	13	1	144	0	0	9	Late
A	13	1	192	0	0	5	Late
A	15	2	96	0	0	4	Late
A	15	2	192	0	1	53	Late
A	15	2	240	0	0	20	Late
A	18	1	72	0	0	14	Late
A	20	1	5	0	0	4	Late
A	20	1	72				Did not show for blood draw
A	20	1	96	0	2	46	Late
A	22	2	1.5	0	0	3	Late
A	23	2	144	0	0	7	Late
A	23	2	192	0	0	8	Late
A	23	2	240	0	0	5	Late
A	24	2	96	0	0	12	Late
A	24	2	144	0	0	47	Late
A	24	2	192	0	0	5	Late
A	25	1	2.5	0	0	3	Late
A	25	1	36	0	0	3	Late
A	25	1	96	0	0	20	Late
A	25	1	144	0	0	6	Late
A	25	1	240	0	0	36	Late
A	26	2	96	0	3	39	Late
A	28	1	72	0	0	10	Late
A	29	1	72	0	0	7	Late
A	31	2	96	0	0	7	Late
A	33	2	192	0	0	3	Late
A	36	2	96	0	1	9	Late
A	36	2	144	0	0	10	Late
A	36	2	192				Did not show for blood draw
A	36	2	240	0	7	46	Late
B	1	2	72	0	0	13	Late

A = Chelsea 25 mg clomipramine HCl capsules
B = Basel (Anafranil) 25 mg clomipramine HCl capsules

File DEVSS.OUT created 30/MAY/95 10:32am by JACKIES. DataBase Ver# 4.53, Internal Ver# 94.01-F04-R04

Attachment # 2 (Cont.)

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Comment
B	1	2	144	0	0	11	Late
B	2	1	240	0	0	8	Late
B	3	1	72	0	0	24	Late
B	3	1	144	0	0	10	Late
B	6	2	72	0	0	3	Late
B	6	2	144	0	1	15	Late
B	6	2	240	0	0	19	Late
B	7	2	144	0	0	15	Late
B	9	2	96	0	0	35	Late
B	9	2	144	0	0	37	Late
B	9	2	192	0	0	11	Late
B	14	1	144	0	0	37	Late
B	14	1	192	0	0	5	Late
B	15	1	96	0	0	20	Late
B	15	1	144	0	0	31	Late
B	15	1	192	0	0	33	Late
B	15	1	240	0	0	31	Late
B	18	2	96	0	0	20	Late
B	18	2	192	0	0	3	Late
B	20	2	96	0	0	35	Late
B	20	2	192	0	0	41	Late
B	22	1	5	0	0	3	Late
B	22	1	36	0	0	6	Late
B	22	1	48	0	0	11	Late
B	22	1	96	0	0	33	Late
B	22	1	144	0	0	5	Late
B	22	1	192	0	0	4	Late
B	22	1	240	0	0	27	Late
B	23	1	0.5	0	0	3	Late
B	23	1	72	0	0	24	Late
B	23	1	96	0	0	21	Late
B	23	1	144	0	0	22	Late
B	23	1	240	0	0	26	Late
B	24	1	96	0	0	15	Late
B	24	1	144	0	0	18	Late
B	24	1	192	0	0	45	Late
B	24	1	240	0	0	26	Late
B	25	2	72	0	2	55	Late
B	25	2	96	0	0	12	Late
B	25	2	144	0	0	58	Late
B	25	2	192	0	0	7	Late
B	26	1	48	0	0	4	Late
B	26	1	72				Did not show for blood draw
B	26	1	192	0	3	10	Late
B	26	1	240	0	0	22	Late
B	27	2	96	0	0	21	Late
B	31	1	12	0	0	15	Late
B	33	1	240	0	0	12	Late
B	35	1	96	0	0	46	Early
B	35	1	144	0	0	7	Late

A = Chelsea 25 mg clomipramine HCl capsules
B = Basel (Anafranil) 25 mg clomipramine HCl capsules

File DEVSS.OUT created 30/MAY/95 10:32am by JACKIES. DataBase Ver# 4.53, Internal Ver# 94.01-F04-R04

Comments/Deficiencies:

1. The in vivo bioequivalence study conducted on the test and the reference products under fasting condition is incomplete.

2. The firm should provide the extraction and derivatization procedures of clomipramine and monodesmethylclomipramine from human plasma before injecting into the

3. The firm should provide analytical conditions.

4. The firm should provide Lot size of the test product on which the in vitro dissolution testing and in vivo bioequivalence study were conducted.

5. The firm did not provide data on monodesmethylclomipramine levels and the corresponding pharmacokinetic parameters of the test and reference products of the study conducted under fed condition.

6. Monodesmethylclomipramine levels of the test and reference products are comparable in the study conducted under fasting condition. However, in some subjects, the carryover effect was observed in Period II. The firm did not performed statistical analysis on monodesmethylclomipramine data and therefore, did not fulfill the Agency drug approval requirements.

7. The comparative in vitro dissolution testing conducted on 25.0 mg, 50 mg and 75.0 mg Clomipramine Hydrochloride Capsule is not acceptable. The firm should be advised to conduct the dissolution testing using the following dissolution conditions:

Apparatus:	USP XXIII Apparatus II (Paddle)
Speed:	RPM 50
Medium:	500 mL 0.1N HCl at 37^{0}C
Tolerances:	% (Q) in 30 minutes
Analytical Procedure:	UV Absorption at ca. 252 nm.

8. The firm has indicated that they have obtained information through Freedom of Information on the New Drug Application (NDA 19-906) for clomipramine, which indicates that AUC and Cmax increase as a linear function of dose between 25 and 75 mg. The firm has been requested by the Division of Bioequivalence to provide this information.

9. The formulations of 25.0 mg, 50 mg and 75.0 mg Clomipramine Capsules are shown to be proportional.

Attachment # 2 (cont.)

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Comment
B	35	1	192	0	0	4	Early
B	36	1	144	0	0	4	Late
B	36	1	192	0	0	13	Late

A = Chelsea 25 mg clomipramine HCl capsules
B = Basel (Anafranil) 25 mg clomipramine HCl capsules

File DEVSS.OUT created 30/MAY/95 10:32am by JACKIES. DataBase Ver# 4.53, Internal Ver# 94.01-P04-R04

6. / Brown, J

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-751 APPLICANT: Chelsea Lab., Inc.

DRUG PRODUCT: Clomipramine Hydrochloride Capsules, 25 mg, 50 mg and 75 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

You should incorporate the dissolution testing into your manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.1N HCl at 37° C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following tentative specification:

Not less than % of the labeled amount of
the drug in the capsule dissolved in minutes

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivale
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 10 1996

Clomipramine Hydrochloride
Capsules, 25 mg, 50 mg and 75 mg
ANDA #74-751
Reviewer: Sikta Pradhan, Ph.D.
WP #74751SA.596

Chelsea Lab., Inc.
Cincinnati, Ohio
Submission Date:
May 28, 1996

REVIEW OF AN AMENDMENT TO A BIOEQUIVALENCE STUDY

Background

Clomipramine hydrochloride is a tricyclic antidepressant. It is used as an anti-obsessional agent. The pharmacologic action is thought to be through its effect on serotonergic neural transmission.

The firm had conducted in vivo bioequivalence studies on the test and the reference products under fed and fasted conditions on 25 mg Clomipramine Hydrochloride Capsules. The studies were found to be incomplete by the Division of Bioequivalence.

This amendment contains the firm's responses to the reviewer's comments made on the submission dated September 19, 1995.

Agency's Comments on the Bioequivalence Study:

1. The firm did not provide the lot size of the test product on which the in vitro dissolution testing and in vivo bioequivalence study were conducted.

2. The firm should provide the extraction and derivatization procedures of clomipramine and monodesmethylclomipramine from human plasma before injecting into the

3. The firm should provide , analytical conditions.

4. The comparative in vitro dissolution testing conducted on 25.0 mg, 50 mg and 75.0 mg Clomipramine Hydrochloride Capsule is not acceptable. The firm should be advised to conduct the dissolution testing using the following dissolution conditions:

Apparatus:	USP XXIII Apparatus II (Paddle)
Speed:	RPM 50
Medium:	500 mL 0.1N HCl at 37^{0}C
Tolerances:	% (Q) in minutes
Analytical Procedure:	UV Absorption at ca. 252 nm.

5. The firm has provided Monodesmethylclomipramine levels of the test and reference products in the study conducted under

fasting condition. The carryover effect was observed in some subjects in Period II. The firm did not perform statistical analysis on monodesmethylclomipramine data.

6. The firm did not provide data on monodesmethylclomipramine levels and the corresponding pharmacokinetic parameters of the test and reference products of the study conducted under fed condition.

Firm's Responses:

1. The firm has reported that the test product had a batch size of capsules.

2. The firm has provided the extraction and derivatization procedures (see attached information - not for release under FOI).

3. The firm has provided analytical conditions (information attached - not for release under FOI).

4. The firm has conducted the acceptable in vitro dissolution testing on 25.0 mg, 50 mg and 75.0 mg Clomipramine Hydrochloride Capsule using the following dissolution conditions:

Apparatus:	USP XXIII Apparatus II (Paddle)
Speed:	RPM 50
Medium:	500 mL 0.1N HCl at 37^{0}C
Tolerances:	% (Q) in minutes
Analytical Procedure:	UV Absorption at ca. 252 nm.

The dissolution testing data are presented below.

Results of In-Vitro Dissolution Testing:

Sampling Test Product: **Clomipramine HCl capsules** Reference Product: **Anafranil**

Times (Min.)	Lot # 2216SQ Strength (mg) 25 Mean % Dissolved	Range	(CV)	Lot # 1T165404 Strength (mg) 25 Mean % Dissolved	Range	(CV)
5	101.4		(2.7)	84.9		(16.9)
10	104.0		(2.4)	103.4		(0.9)
15	103.4		(2.4)	104.0		(1.0)
30	104.5		(2.2)	104.3		(0.7)
45	105.2		(2.3)	104.3		(1.4)

Sampling Times (Min.)	Test Product Lot # 2217SQ Strength (mg) 50 Mean % Dissolved	Range	(CV)	Reference Product Lot # 1T156500 Strength (mg) 50 Mean % Dissolved	Range	(CV)
5	95.9		(7.4)	99.9		(4.0)
10	104.8		(2.2)	104.5		(2.7)
15	105.3		(2.0)	105.1		(2.4)
30	105.5		(2.0)	105.4		(2.2)
45	105.6		(2.1)	105.3		(2.3)

Sampling Times (Min.)	Test Product Lot # 2218SQ Strength (mg) 75 Mean % Dissolved	Range	(CV)	Reference Product Lot # 1T158083 Strength (mg) 75 Mean % Dissolved	Range	(CV)
5	73.9		(12.2)	90.4		(9.0)
10	100.4		(2.5)	101.4		(1.7)
15	101.1		(1.9)	102.0		(1.9)
30	101.9		(2.1)	101.8		(2.1)
45	102.1		(2.1)	101.8		(2.2)

5. To respond the Agency's comment on the carry over effect, the firm has indicated that there were 2/34 subjects who had concentrations of monodesmethylclomipramine above the limit of quantitation (LOQ) of 0.5 ng/mL at the start of period 2. Subject No. 7 received the test formulation in period 1 and had a predose concentration of 0.56 ng/mL at the start of period 2 while subject No. 8 received the reference formulation in period 1 and had a predose concentration of 0.65 ng/mL at the start of period 2. These concentrations were slightly above the LOQ.

6. At the Agency's request, the firm has provided the pharmacokinetic/statistical analyses of monodesmethylclomipramine levels obtained after administration of both the test and reference products under fasting condition. Summary of results are presented in Appendix #1 and in Table 1A (attached). These results show that LnC_{max} and $LnAUC_{inf}$ pass the usual bioequivalence criterion of 80-125% of 90% CI, but $LnAUC_{0-t}$ (69-102%) does not pass the same criterion.

7. The firm has stated that one subject (subject# 30) had only 5 measurable concentrations (up to 12 hours) of the metabolite after administration of the test formulation and thus AUC_{0-t} could be evaluated only up to 12 hours, compared to the $LnAUC_{0-t}$ measured over 96 hours for the reference formulation. No such problems were observed in the case of parent compound. The firm has further indicated that after excluding subject #30, $LnAUC_{0-t}$ would meet the usual bioequivalence criterion of 80-125% of 90% CI. Summary of results are presented in Table 3A (attached).

8. The firm has also conducted a study on clomipramine test and reference products in 16 subjects under fed condition and has provided the statistical data and pharmacokinetic parameters of clomipramine and monodesmethylclomipramine (Appendix #2 and Tables 1B and 2B attached). The results presented in Table 5 (see Appendix #2) of original review of submission dated September 19, 1995 show that the pharmacokinetic parameter, $LnAUC_{0-t}$ of clomipramine (data on 16 subjects) does not meet the bioequivalence criterion of ± 20% difference in test and reference values, but it meets the criterion for the metabolite.

9. In a separate analysis (see Table 6 of original review of submission dated September 19, 1995, presented in Appendix #3), the firm has excluded the data of two subjects (#22 and #23) on the basis of vomiting within 24 hours of drug ingestion and recalculated pharmacokinetic parameters for clomipramine but not for monodesmethylclomipramine. It should be pointed out here that, if the exclusion criterion was mentioned in the study protocol, it is acceptable to exclude any subject's data from the final data analysis. However, such subjects should be excluded for all analyses, i.e. the parent compound and metabolite.

10. The firm has provided no explanation for using Residual effects (RESIDA and RESIDB) in their statistical model.

11. The period designation should reflect the actual day that a treatment was received. If there were add-on subjects, then there should be more than three levels of PERIOD in a three-way-crossover study design. The period should always be examined, even though all blood samples were assayed together. In this study, Group I started on Feb. 22, 1995 and three weeks later, Group II started on April 21, 1995. The preferred Model for statistical analysis of this study should be:

```
Model Y = Seq Subj(Seq) Per Group*Per Trt;
```

The analysis should allow to test for the possibility that the period effects for Group I was not the same as the period effects for Group II.

12. The firm did not provide any verbal explanation in the result-section. The firm should be advised to present the study data with proper explanations in future submissions.

Deficiency/Comments:

1. The in vivo Bioequivalence studies conducted under fasted condition by Chelsea Laboratories, Inc. on its 25 mg Clomipramine Hydrochloride Capsules versus the listed reference product, Anafranil® Capsule, 25 mg has been found to be unacceptable as $LnAUC_{0-t}$ of monodesmethylclomipramine metabolite (Table 1A) does not meet the bioequivalence criterion of 80-125% of 90% CI.

2. Exclusion of data of subject #30 is not acceptable. Explanation is required, why there were only 5 measurable concentration for metabolite of subject #30 on the test product. If the metabolite levels really dropped below the LOQ after 12 hours, the question would be, why did that happen with the test product only?

3. The bioequivalence guidance (July 1992) indicates that if a subject is to be deleted from the analysis as an "outlier", a justification must be provided. This justification is to be based on valid scientific reasons.

4. The fed study conducted in 16 subjects does not meet the bioequivalence criterion of ±20% difference in pharmacokinetic parameters for clomipramine of the test and reference products.

Recommendations:

1. The in vivo Bioequivalence studies conducted (under fed and fasted conditions) by Chelsea Laboratories, Inc. on its 25 mg Clomipramine Hydrochloride Capsules, Lot # 2216 SQ versus the listed reference product, Anafranil® Capsule, 25 mg, manufactured by Basel Pharmaceuticals has been found to be unacceptable by the Division of Bioequivalence for the reasons stated in Deficiency/Comments #1 - #4 above.

2. The waiver of in vivo bioequivalence study on Clomipramine Hydrochloride 50 mg and 75 mg Capsules has been denied.

/S/

Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ 6/28/96

Concur: /S/ Date: 7/10/96
for Keith K. Chan, Ph. D.
Director, Division of Bioequivalence

cc: ANDA # 74-751 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Pradhan), Drug File, Division File.

SP/06-26-96/X:\wpfile\Pradhan\74751SA.596

Appendix #1

Mean Pharmacokinetic Parameters for Monodesmethylclomipramine in Plasma (Fasting Study)

Parameters (Arithmetic Means)	Test(A) (Subj=N=33)	Ref.(B) (Subj=N=33)	100xA/B
$LnAUC_{0-T}$ (ng.hr/mL)	125.34 (176*)	149.94 (115)	84
$LnAUC_{0-inf}$ (ng.hr/mL)	222.18 (103) (N=30)	231.11 (92) (N=31)	96
LnC_{MAX} (ng/mL)	2.9038 (50)	3.0489 (46)	95

Parameters (Using LSM)	Test(A)	Ref.(B)	100xA/B	90% C.I.
$LnAUC_{0-T}$	126.04	150.26	84	**69; 102**
$LnAUC_{0-inf}$	213.78	230.16	93	**80; 107**
LnC_{MAX}	2.9145	3.0577	95	**87; 105**

* Coefficient of Variation (%)
LSM - Least Squares Means
Total Number of Subjects = N

Appendix #2

Table 5
Mean Pharmacokinetic Parameters of Clomipramine
(Fed Study; N=16)

Parameters (arithmetic means)	Test(A) Fasted	Test(B) Fed	REF.(C) Fed	(B/C)	(B/A)
AUC_{0-T} (ng.hr/mL)	201.0 (41)* (N=15)	210.9 (51) (N=16)	247.6 (26) (N=15)	0.85	1.05
AUC_{0-inf} (ng.hr/mL)	230.3 (41) (N=13)	246.6 (42) (N=15)	271.3 (26) (N=15)	0.91	1.07
C_{MAX} (ng/mL)	13.0 (32) (N=15)	12.1 (46) (N=16)	13.38 (17) (N=15)	0.90	0.93
T_{max} (hour)	3.83 (27) (N=15)	5.09 (25) (N=16)	5.27 (27) (N=15)		
t1/2 (hour)	21.84(36) (N=13)	21.9 (44) (N=15)	21.83 (38) (N=15)		
KE (1/hour)	0.036(38) (N=13)	0.037(37) (N=15)	0.036 (38) (N=15)		

Log-Transformed data using LSM

Parameters	Test(B) Fed	Ref.(C) Fed	Test Mean (geometric)	Ref. Mean (geometric)	Test/Ref.(%)
$LAUC_{0-T}$	5.16660405	5.48438787	175.32	240.90	72.8
$LAUC_{0-inf}$	5.44847885	5.54411286	232.40	255.73	90.9
LC_{MAX}	2.35702702	2.55922172	10.56	12.92	81.7

Subject Nos. 22 & 23 (who vomited within 24 hours of drug administration) were included in data analysis.

Mean Pharmacokinetic Parameters for Monodesmethylclomipramine in Plasma (Fed Study; N=16)

Parameters (Arithmetic Means)	Test(A) Fasted	Test(B) Fed	Ref(C) Fed	(B/C)%	(A/B)%
$LnAUC_{0-T}$ (ng.hr/mL)	169.69(82*)	182.84(76)	201.25(65)	91	93
$LnAUC_{0-inf}$ (ng.hr/mL)	216.92(72)	236.50(69)	247.07(59)	96	92
LnC_{MAX} (ng/mL)	3.2927(37)	3.2639(37)	3.3719(34)	97	101

Parameters (Using LSM)	Test(A) Fasted	Test(B) Fed	Ref(C) Fed	(B/C)%
$LnAUC_{0-T}$	176.82	179.06	198.86	90
$LnAUC_{0-inf}$	222.95	234.69	244.12	96
LnC_{MAX}	3.4095	3.2307	3.3060	98

* Coefficient of Variation (%)
LSM - Least Squares Means
Total Number of Subjects = N

Appendix #3

Table 6
Mean Pharmacokinetic Parameters of Clomipramine
(N=14)

Parameters (arithmetic means)	Test(A) Fasted	Test(B) Fed	REF.(C) Fed	(B/C)	B/A)
AUC_{0-T} (ng.hr/mL)	187.5 (40)* (N=13)	209.1 (40) (N=14)	232.2 (23) (N=13)	0.90	1.11
AUC_{0-inf} (ng.hr/mL)	212.3 (40) (N=11)	231.5 (38) (N=14)	255.4 (23) (N=13)	0.91	1.09
C_{MAX} (ng/mL)	12.71 (34) (N=13)	12.26 (38) (N=14)	13.15 (17) (N=13)	0.93	0.96
T_{max} (hour)	3.64 (27) (N=13)	5.11 (26) (N=14)	5.23 (29) (N=13)		
t1/2 (hour)	19.96(32) (N=11)	20.63(41) (N=14)	20.04(35) (N=13)		
KE (1/hour)	0.038(34) (N=11)	0.038(34) (N=14)	0.039(35) (N=13)		

Log-Transformed data using LSM

Parameters	Test(B) Fed	Ref.(C) Fed	Test Mean (geometric)	Ref. Mean (geometric)	Test/Ref.(%)
$LAUC_{0-T}$	5.261289	5.397548	192.73	220.86	87
$LAUC_{0-inf}$	5.373947	5.494433	215.71	243.33	89
LC_{MAX}	2.457444	2.510222	11.67	12.30	95

Subject Nos. 22 & 23 were withdrawn from statistical analysis.

Table 1A
Project No: 920438
Summary of Results - Monodesmethylclomipramine in Plasma
Pharmacokinetic Parameters
(N = 33)

	ln AUC 0-12* (ng·h/mL)	ln AUC 0-t* (ng·h/mL)	ln AUCinf* (ng·h/mL)	ln Cmax* (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)
Chelsea (A)							
Mean	23.398	125.344	222.176	2.9038	9.030	0.01531	57.83
CV	56.2	176.1	103.4	50.5	82.8	48.5	60.0
n	33	33	30	33	33	30	30
Basel (B)							
Mean	25.016	149.937	231.114	3.0489	8.030	0.01574	59.82
CV	43.2	114.6	92.0	46.5	68.0	42.9	78.4
n	33	33	31	33	33	31	31
Least-Squares Means							
Chelsea (A)	23.537	126.039	213.778	2.9145			
Basel (B)	25.143	150.259	230.157	3.0577			
Ratio of Least-Squares Means (A/B)%	93.6	83.9	92.9	95.3			
90% Confidence Intervals (A/B)%							
lower limit:	85.3%	69.2%	80.4%	86.8%			
upper limit:	102.7%	101.7%	107.2%	104.7%			
p-Value (ANOVA)							
A vs B	0.2377	0.1326	0.3897	0.3919			
Period	0.8602	0.7458	0.9384	0.8762			
Sequence	0.4447	0.8156	0.3654	0.6401			

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See statistics report for details on calculation of parameters
Note: Data for Subject No. 1 were excluded
PhAST STAB 2.3-000

SET3

Table 3A
Project No: 920438
Summary of Results - Monodesmethylclomipramine in Plasma
Pharmacokinetic Parameters
(N = 32)

	ln AUC 0-12* (ng·h/mL)	ln AUC 0-t* (ng·h/mL)	ln AUCinf* (ng·h/mL)	ln Cmax* (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)
Chelsea (A)							
Mean	24.445	138.008	241.141	3.0280	9.125	0.01435	59.26
CV	49.4	146.0	85.1	43.7	83.0	37.5	58.0
n	32	32	29	32	32	29	29
Basel (B)							
Mean	25.007	150.023	232.654	3.0473	8.031	0.01573	60.39
CV	43.9	117.4	93.9	47.3	69.1	43.7	78.8
n	32	32	30	32	32	30	30
Least-Squares Means							
Chelsea (A)	24.485	137.766	232.140	3.0284			
Basel (B)	25.097	150.245	232.654	3.0537			
Ratio of Least-Squares Means (A/B)%	97.6	91.7	99.8	99.2			
90% Confidence Intervals (A/B)%							
lower limit:	92.5%	82.8%	93.7%	93.5%			
upper limit:	103.0%	101.5%	106.2%	105.2%			
p-Value (ANOVA)							
A vs B	0.4419	0.1581	0.9523	0.8140			
Period	0.3272	0.3937	0.0418	0.3827			
Sequence	0.5947	0.9900	0.2105	0.8181			

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See statistics report for details on calculation of parameters
Note: Data for Subject Nos. 1 and 30 were excluded
PhAST STAB 2.3-000

SET3A

Table 2B
Project No: 940494
Summary of Results - Monodesmethylclomipramine in Plasma
Pharmacokinetic Parameters
(N = 16)

	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)
Chelsea (fasted) (A)			
Mean	223.06	271.91	3.497
CV	90.0	83.0	36.8
n	16	16	16
Chelsea (fed) (B)			
Mean	230.08	289.10	3.466
CV	79.0	76.1	36.7
n	16	16	16
Basel (fed) (C)			
Mean	240.93	288.39	3.549
CV	70.6	66.9	33.7
n	16	16	16
Least-Squares Means			
Chelsea (fasted) (A)	228.48	274.85	3.605
Chelsea (fed) (B)	226.14	286.64	3.411
Basel (fed) (C)	233.15	281.26	3.492
Ratio of Least-Squares Means			
(B/A)%	99.0	104.3	94.6
(B/C)%	97.0	101.9	97.7

See Statistics Report for details on calculation of parameters.
PhAST STAB 2.3-000

FDADEF

Table 18
Project No: 940494
Summary of Results - Monodesmethylclomipramine in Plasma
Pharmacokinetic Parameters
(N = 16)

	ln AUC 0-t* (ng·h/mL)	ln AUCinf* (ng·h/mL)	ln Cmax* (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)
Chelsea (fasted) (A)						
Mean	169.695	216.921	3.2927	8.719	0.01669	45.00
CV	82.1	72.3	36.8	92.8	28.9	30.9
n	16	16	16	16	16	16
Chelsea (fed) (B)						
Mean	182.843	236.498	3.2639	15.188	0.01607	48.03
CV	75.9	68.6	36.7	74.1	30.4	39.0
n	16	16	16	16	16	16
Basel (fed) (C)						
Mean	201.247	247.067	3.3719	13.688	0.01680	44.84
CV	64.9	58.7	33.8	76.9	27.3	33.4
n	16	16	16	16	16	16
Least-Squares Means						
Chelsea (fasted) (A)	176.824	222.950	3.4095			
Chelsea (fed) (B)	179.057	234.686	3.2307			
Basel (fed) (C)	198.858	244.122	3.3060			
Ratio of Least-Squares Means						
(B/A)%	101.3	105.3	94.8			
(B/C)%	90.0	96.1	97.7			

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See Statistics Report for details on calculation of parameters.
PhAST STAB 2.3-000

FDADEF

0001137

Clomipramine Hydrochloride
Capsules, 25 mg, 50 mg and 75 mg
ANDA #74-751
Reviewer: Sikta Pradhan, Ph.D.
XWP #74751SA.298

Chelsea Lab., Inc.
Cincinnati, Ohio
Submission Date:
February 27, 1998
July 6, 1998

REVIEW OF AN AMENDMENT TO A BIOEQUIVALENCE STUDY

Background

Clomipramine hydrochloride is a tricyclic antidepressant. It is used as an anti-obsessional agent. The pharmacologic action is thought to be through its effect on serotonergic neural transmission.

The firm had conducted in vivo bioequivalence studies on the test and the reference products under fed and fasted conditions on 25 mg Clomipramine Hydrochloride Capsules. The fasting study was acceptable but the study was found to be incomplete by the Division of Bioequivalence.

This amendment contains the firm's responses to the reviewer's comments made on the submission dated January 20, 1998.

Agency's Comments on the Bioequivalence Study:

1. The sponsor has stated in the clinical report that, of 18 male volunteers (group I) who originally enrolled in the study, six subjects (#4, #9, #13, #14, #17, #18) did not complete the study. The firm has also stated that, 3 subjects of 6 additional subjects enrolled (group II) could not complete the study. Thus a total of 15 subjects completed the study (1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 15, 16, 19, 22, 23). The firm has also specified in the protocol (Project No. 940494) under the "statistical Analysis" section that subjects who vomited within 24 hours of drug administration were to be excluded from the analysis, and consequently, subjects No. 22 and 23 should be excluded from the fed study. Hence, the total number of subjects completing the study should be 13.

2. Furthermore, the sponsor had reported (attached memo in Appendix #3) that clomipramine levels were not estimated correctly from plasma samples of subject #3. This subject's concentration data is therefore incomplete and his data was excluded from statistical and pharmacokinetic analysis. Therefore, both the pharmacokinetic and statistical analysis should be conducted on plasma data of 12 and 13 subjects for clomipramine and monodesmethylclomipramine, respectively.

3. However, the results of the fed study submitted by the sponsor previously as well as submitted in the current amendment (Appendix #4, attached) were derived from 16, 15 , 14 and 12 subjects' plasma data without providing any explanation. These results are not acceptable to the Division of Bioequivalence, and consequently, the bioequivalence study under fed conditions on Clomipramine Hydrochloride, 25 mg capsules remained unacceptable.

Firm's Responses:

1 The firm has reported that, of the 24 subjects dosed, the total number of subjects completing all three periods is 15. Subjects No. 4, 9, 13, 14, 17, 18 (Group 1) and 20, 21 and 24 (Group 2) did not complete all three periods of the study.

2. However, the study protocol specified that, data from only those subjects who completed at least two periods of the study will be included in the statistical analysis. Therefore, subjects No. 4, 14, and 24 should be included in the statistical analysis.

3. The protocol has also specified that the comparisons of interest are, B vs A and B vs C, but not A vs C. Since subject No.4 completed two periods of the study, Regimens A and C, samples from this subject were not analyzed. Hence the total number of subjects included in the statistical analysis should be 15+2 (subjects #14, #24).

4. It was also in the protocol that those subjects who vomited or experienced diarrhea within 24 hours of drug administration will be excluded from the statistical analysis. Therefore, subjects No. 22 & 23 should be

excluded and the total number of subjects for statistical analysis should be 17 - 2.

5. Of these 15 subjects, one had incomplete clomipramine data (but not for metabolite). Clomipramine concentration data for subject #3 were incomplete due to repeated analytical rejection of the standard curves. Hence, the total number of subjects included in the statistical analyses for **clomipramine is 14 and for monodesmethyl-clomipramine is 15** (see Tables 1 & 2 attached). The results of the pharmacokinetic parameters are shown below:

Table 3
Mean Pharmacokinetic Parameters of Clomipramine
(N=14)

Parameters (arithmetic means)	Test(A) Fasted	Test(B) Fed	REF.(C) Fed	(B/C)	(B/A)
AUC_{0-T} (ng.hr/mL)	187.5 (40)* (N=13)	209.1 (40) (N=14)	232.2 (23) (N=13)	0.90	1.11
AUC_{0-inf} (ng.hr/mL)	212.3 (40) (N=11)	231.5 (38) (N=14)	255.4 (23) (N=13)	0.91	1.09
C_{MAX} (ng/mL)	12.71 (34) (N=13)	12.26 (38) (N=14)	13.15 (17) (N=13)	0.93	0.96
T_{max} (hour)	3.64 (27) (N=13)	5.11 (26) (N=14)	5.23 (29) (N=13)		
t1/2 (hour)	19.96(32) (N=11)	20.63(41) (N=14)	20.04(35) (N=13)		
KE (1/hour)	0.038(34) (N=11)	0.038(34) (N=14)	0.039(35) (N=13)		

Log-Transformed data using LSM

Parameters	Test(B) Fed	Ref.(C) Fed	Test Mean (geometric)	Ref. Mean (geometric)	Test/Ref.(%)
$LAUC_{0-T}$	5.261289	5.397548	192.73	220.86	87
$LAUC_{0-inf}$	5.373947	5.494433	215.71	243.33	89
LC_{MAX}	2.457444	2.510222	11.67	12.30	95

* Coefficient of Variation (%)
LSM - Least Squares Means
N = Total Number of Subjects

Table 4

Mean Pharmacokinetic Parameters for Monodesmethylclomipramine in Plasma

(Fed Study; N=15)

Parameters (Arithmetic Means)	Test(A) Fasted	Test(B) Fed	Ref© Fed	(B/C)%	(A/B)%
$LnAUC_{0-T}$ (ng.hr/mL) N=14	168.71(88*)	179.81(79)	198.30(70)	91	94
$LnAUC_{0-inf}$ (ng.hr/mL) N=15	215.15(78)	233.31(71)	241.89(63)	96	92
LnC_{MAX} (ng/mL) N=14	3.3392(39)	3.3030(38)	3.4363(36)	96	101

Parameters (Using LSM)	Test(A) Fasted	Test(B) Fed	Ref© Fed	(B/C)%
$LnAUC_{0-T}$	177.57	177.68	197.15	90
$LnAUC_{0-inf}$	222.89	232.22	240.59	96
LnC_{MAX}	3.4604	3.2962	3.3578	98

* Coefficient of Variation (%)
LSM - Least Squares Means
N = Total Number of Subjects

Formulations:

The compositions of Clomipramine 25.0 mg, 50.0 mg and 75.0 mg Capsules are presented below:

Ingredients	Strengths (mg/ capsule)		
	25.0 mg Cap*	50.0 mg Cap**	75.0 mg Cap***
/Clomipramine HCl BP	25.0	50.0	75.0
✓Pregelatinized Starch, NF (Starch 1500)			
✓Pregelatinized Starch, NF (Starch 1500)			
✓Colloidal Silicon Dioxide, NF (Cab-O-Sil)			
✓Magnesium Stearate, NF			
Total Weight			

* Description: #4 Lt. Brown Op/White Op Hard Gelatin Capsule Imprinted RUGBY 5585, filled with white powder.

** Description: #2 Lt. Blue Op/White Op Hard Gelatin Capsule Imprinted RUGBY 5586, filled with white powder.

*** Description: #1 Lt. White Op/White Op Hard Gelatin Capsule Imprinted RUGBY 5587, filled with white powder.

The formulations of 25.0 mg, 50 mg and 75.0 mg Clomipramine Capsules are shown to be proportional.

Comments:

1. The in vivo Bioequivalence studies conducted under fed conditions by Chelsea Laboratories, Inc. on its 25 mg Clomipramine Hydrochloride Capsules, Lot # 2216 SQ versus the listed reference product, Anafranil^{R} Capsule, 25 mg, manufactured by Basel Pharmaceuticals has been found acceptable.

2. The firm had previously conducted an acceptable study under fasting conditions on its 25 mg Clomipramine Hydrochloride Capsules, Lot # 2216, comparing it with the listed reference product, Anafranil^{R} Capsule, 25 mg, manufactured by Basel Pharmaceuticals.

3. The firm has conducted the acceptable in vitro dissolution testing on 25.0 mg, 50 mg and 75.0 mg Clomipramine Hydrochloride Capsule

using the following dissolution conditions:

Apparatus:	USP XXIII Apparatus II (Paddle)
Speed:	RPM 50
Medium:	500 mL 0.1N HCl at 37°C
Tolerances:	% (Q) in minutes
Analytical Procedure:	UV Absorption at ca. 252 nm.

(The dissolution testing data were presented in the review of the submission dated May 28, 1996.)

4. The formulations of 25.0 mg, 50 mg and 75.0 mg Clomipramine Capsules were shown to be proportional.

Recommendations:

1. The in vivo Bioequivalence studies conducted (under fed and fasted conditions) by Chelsea Laboratories, Inc. on its 25 mg Clomipramine Hydrochloride Capsules, Lot # 2216 SQ versus the listed reference product, Anafranil[R] Capsule, 25 mg, manufactured by Basel Pharmaceuticals has been found acceptable by the Division of Bioequivalence. The study demonstrates that 25 mg Clomipramine Hydrochloride Capsule of Chelsea Laboratories, Inc. is bioequivalent to the reference product, Anafranil[R] Capsule, 25 mg manufactured by Basel Pharmaceuticals.

2. The dissolution testings conducted by Chelsea Laboratories, Inc. on its test product, Clomipramine Hydrochloride Capsule 25 mg, 50 mg and 75 mg Capsules, lot #2216SQ, lot #2217SQ and lot #2218SQ, respectively, are acceptable.

   The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.1N HCl at 37° C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

Not less than % of the labeled amount of the drug in the capsule dissolved in minutes.

3. The formulation for the 50 mg and 75 mg strengths are proportionally similar to the 25 mg strength of the test product which underwent bioequivalency testing. The waivers of in vivo bioequivalence study requirements for the 50 mg and 75 mg capsules of the test product are granted. The 50 mg and 75 mg capsules of the test product are therefore deemed bioequivalent to the reference product, Anafranil[R], 50 mg and 75 mg Capsules, respectively, manufactured by Basel Pharmaceuticals.

/S/

Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- /S/ ---------- 7/9/98

Concur: /S/ Date: 7/9/98

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: AND # 74-751 (original, duplicate), HAD-652 (Huang, Pradhan), HAD-650 (Director),Drug File, Division File.

Draft Date/7-6-98//X:\wpfile\Pradhan\74751SA.298

Table 1
Project No. 940494
Clomipramine Data

	Subject Outcome	Subjects included in Definitive Dataset (excluding subjects who vomited)	Subjects included in Supplementary Dataset (including subjects who vomited)
GROUP 1 18 subjects (1-18)	Completed 3 periods (i.e. completed the study; samples analyzed) Subjects No. 1, 2, 3*, 5-8, 10-12, 15, 16 (n = 12)	1, 2, 5-8, 10-12, 15, 16	1, 2, 5-8, 10-12, 15, 16
	Completed 2 periods (comparison of interest; samples analyzed) Subject No. 14	14	14
	Completed 2 periods (not comparison of interest; samples not analyzed) Subject No. 4		
	Completed 1 period only (samples not analyzed) Subjects No. 9, 13, 17, 18		
GROUP 2 6 subjects (19-24)	Completed 3 periods (i.e completed the study; samples analyzed) Subjects No. 19, 22, 23 (n = 3)	19	19, 22, 23
	Completed 2 periods (comparison of interest; samples analyzed) Subject No. 24	24	24
	Completed 1 period only (samples not analyzed) Subjects No. 20, 21		
	Number of subjects completing the study: 15 (n = 12 + n = 3)	Number of subjects in dataset: n = 14	Number of subjects in dataset: n = 16

* Clomipramine concentration data for Subject No. 3 were incomplete due to repeated analytical rejection of the standard curves; therefore, data for this subject were excluded from pharmacokinetic and statistical analyses.

Table 2
Project No. 940494
Monodesmethylclomipramine Data

	Subject Outcome	Definitive Dataset (excluding subjects who vomited)	Supplementary Dataset (including subjects who vomited)
GROUP 1 18 subjects (1-18)	Completed 3 periods (i.e. completed the study; samples analyzed) Subjects No. 1-3, 5-8, 10-12, 15, 16 (n = 12)	1-3, 5-8, 10-12, 15, 16	1-3, 5-8, 10-12, 15, 16
	Completed 2 periods (comparison of interest; samples analyzed) Subjects No. 14	14	14
	Completed 2 periods (not comparison of interest; samples not analyzed) Subject No. 4		
	Completed 1 period only (samples not analyzed) Subjects No. 9, 13, 17, 18		
GROUP 2 6 subjects (19-24)	Completed 3 periods (i.e completed the study; samples analyzed) Subjects No. 19, 22, 23 (n = 3)	19	19, 22, 23
	Completed 2 periods (comparison of interest; samples analyzed) Subject No. 24	24	24
	Completed 1 period only (samples not analyzed) Subjects No. 20, 21		
	Number of subjects completing the study: 15 (n = 12 + n = 3)	Number of subjects in dataset: n = 15	Number of subjects in dataset: n = 17

JAN 2 1998

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 74-751 APPLICANT: Chelsea Laboratories, Inc.

DRUG PRODUCT: Clomipramine Hydrochloride Capsules, 25, 50, and 75 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The Division of Bioequivalence has no further questions regarding the fasting study at this time.

2. You have indicated in the original report (dated September 19, 1995) as well as in the current amendment (dated January 20, 1997), that the total number of subjects completing the fed study were 15 (N1=12, N2=3, in two groups). As specified in the protocol (Project No. 940494), under the "statistical Analysis" section, subjects who vomited within 24 hours of drug administration were to be excluded from the analysis, and therefore, on that basis, subjects No. 22 and 23 should be excluded from the fed study. Hence, the total number of subjects completing the study should be 13.

3. Furthermore, you have reported that clomipramine levels were not estimated correctly from plasma samples of subject #3. This subject's concentration data is therefore incomplete and his data was excluded from statistical and pharmacokinetic analysis. Therefore, both the pharmacokinetic and statistical analysis should be conducted on plasma data of 12 and 13 subjects for clomipramine and monodesmethyl-clomipramine, respectively. However, the results of the fed study submitted previously, as well as the study submitted in the current amendment were derived from 16, 15, 14, and 12 subjects' plasma data without providing any explanation. These results are not acceptable to the Division of Bioequivalence, and consequently, the bioequivalence study under fed conditions on Clomipramine Hydrochloride, 25 mg capsules remains unacceptable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Clomipramine Hydrochloride
Capsules, 25 mg, 50 mg and 75 mg
ANDA #74-751
Reviewer: Sikta Pradhan, Ph.D.
WP #74751SA.197

Chelsea Lab., Inc.
Cincinnati, Ohio
Submission Date:
January 20, 1997
June 6, 1997
August 20. 1997

REVIEW OF AN AMENDMENT TO A BIOEQUIVALENCE STUDY

Background

Clomipramine hydrochloride is a tricyclic antidepressant. It is used as an anti-obsessional agent. The pharmacologic action is thought to be through its effect on serotonergic neural transmission.

The firm had conducted in vivo bioequivalence studies on the test and the reference products under fed and fasted conditions on 25 mg Clomipramine Hydrochloride Capsules. The fasting study was found to be unacceptable by the Division of Bioequivalence as $LnAUC_{0-t}$ of monodesmethylclomipramine metabolite in fasting study did not meet the bioequivalence criterion of 80-125%. The fed study also did not meet the bioequivalence criterion of $\pm$ 20%.

In the previous amendment (submission dated May 28,1996), the firm reported that in the bioequivalence study under fasting condition, one subject (subject# 30) had only 5 measurable concentrations (up to 12 hours) of the metabolite after administration of the test formulation and thus AUC_{0-t} could be evaluated only up to 12 hours, compared to the $LnAUC_{0-t}$ measured over 96 hours for the reference formulation. No such problems were observed in the case of the parent compound. The firm further indicated that after excluding subject #30, $LnAUC_{0-t}$ would meet the usual bioequivalence criterion of 80-125% of 90% CI. The firm therefore, requested the Agency to exclude the data of subject #30 and approve the application. This amendment was found unacceptable by the Agency.

In the current amendments (submission dated January 20,1997 and June 6, 1997), the firm has submitted the data of a retest (including drug administration, blood collection and data analysis) of subject #30 (claimed as an outlier) and three other subjects (#2, #8 and #22) who previously participated in the original bioequivalence study under fasting conditions (study

protocol No. 920438). The firm has also reported the recalculated mean pharmacokinetic parameters of the study conducted under fed conditions and requested for reconsideration.

Objective of the Bioequivalence Study of Four Subjects under Fasting Conditions:

The firm's objective of this study (Protocol #920438A) was to evaluate the pharmacokinetic data for 4 subjects (including Subject #30) who previously completed the original bioequivalence study under fasting conditions (Protocol #920438). The pharmacokinetic data of each subject from this study were then compared with the corresponding subject's data of the previous study in order to determine if Subject #30 was an "outlier".

Method:

The sponsor has reported that the experimental designs (except total number of subjects involved in the study) of the current study and that originally conducted under fasting conditions were identical.

Results:

Individual plasma concentration data for Subjects No. 2, 8, 22 and 30 for original study (Project #920438) and the repeat study (Project #920438A) are presented in Appendix #1 (attached). Individual subject profiles for both studies are included in the Appendix #2 (attached). Regression curves for AUC_{0-t} (metabolite only) of the repeat study for the test and reference are presented in Figures 1 and 2, respectively (attached in Appendix 2). The results indicated that the r^2 and slope values are closer to unity for the reference : reference comparison than for the test : test comparison. After removal of data for subject #30, the values were also closer to unity. However, it is not known, whether same results will also be observed with other parameters (C_{max} or AUC_{0-inf}), as the firm did not provide any regression analysis, for C_{max} or AUC_{0-inf} of the metabotite and, for all three parameters of the parent compound.

The pharmacokinetic parameters, AUC_{0-t}, AUC_{0-inf} and C_{max} of each of 4 subjects for the test (A) and reference (B) products, along with the percentage difference, for monodesmethylclomipramine and clomipramine are presented in Table 1.

Table 1. Pharmacokinetic Parameters

Monodesmethylclomipramine results for AUC(0-t)
ng.hr/mL

	Project #920438A (repeat)				Project #920438 (original)					
Subj#	Test (A)	Ref. (B)	A/B%	(Diff. of A&B) %	Test (A)	Ref. (B)	A/B%	Mean Test/Ref % of 33 Subjects	(Diff. of A&B)%	%Change of A/ B between original and repeat assays
2								94.16 Range:	7.6	20.5
8									13	11.9
22									-1.2	6.6
30									-96.1	84.4

Monodesmethylclomipramine results for AUC(0-inf)
ng.hr/mL

	Project #920438A (repeat)				Project #920438 (original)					
Subj.#	Test (A)	Ref. (B)	A/B%	(Diff. of A&B) %	Test (A)	Ref. (B)	A/B%	Mean Test/Ref % of 30 Subjects	(Diff. of A&B) %	%Change of A / B between original and repeat assays
2								99.17 Range:	7.9	24.0
8									-4.9	20.6
22									-8.3	13.6
30									-89.1	77.9

Monodesmethylclomipramine results for C_{max} (ng/mL)

	Project #920438A (repeat)				Project #920438 (original)					
Subj.#	Test (A)	Ref. (B)	A/B%	(Diff. of A&B) %	Test(A)	Ref.(B)	A/B%	Mean Test/Ref % of 33 Subjects	(Diff. of A&B) %	%Change of A / B between original and repeat assays
2								99.02 Range:	19.1	54.7
8									26.8	11.3
22									9.6	4.2
30									-75.5	55.6

Clomipramine results for AUC(0-t)
ng.hr/mL

	Project #920438A (repeat)				Project #920438 (original)					
Subj.#	Test (A)	Ref. (B)	A/B%	(Diff. of A&B) %	Test (A)	Ref. (B)	A/B%	Mean Teas/Ref % of 32 Subjects	(Diff. of A&B) %	%Change of A / B between original and repeat assays
2								102.07 Range:	0.0	17.3
8									-2.4	18.6
22									-37.4	55.2
30									-71.6	70.7

Clomipramine results for AUC(0-inf)
ng.hr/mL

	Project #920438A (repeat)				Project #920438 (original)					
Subj.#	Test (A)	Ref. (B)	A/B%	(Diff. of A&B) %	Test (A)	Ref. (B)	A/B%	Mean Test/Ref % of 29 Subjects	(Diff. of A&B) %	%Change of A/ B between original and repeat assays
2								100.91 Range:	-0.5	10.9
8									-2.2	20.7
22									-35.2	54.0
30									-71.7	72.3

Clomipramine results for Cmax (ng/mL)

	Project #920438A (repeat)				Project #920438 (original)					
Subj.#	Test (A)	Ref. (B)	A/B%	(Diff .of A&B) %	Test (A)	Ref. (B)	A/B%	Mean Test/Ref % of 32 Subjects	(Diff. of A&B) %	%Change of A/ B between original and repeat assays
2								99.52 Range:	10.9	59.2
8									-11.4	12.4
22									-25.8	15.3
30									-61.6	55.1

The repeat study (P#920438A) indicated that the pharmacokinetic (PK) parameter levels of subject #30 following the redosing of the test(A) and reference(B) products were more similar as opposed to the study P#920438 (original) where **the test levels of subject #30 were considerably lower than the reference levels.** However, it should be noted here that a similar result in the case of subject #22 and an opposite result in subject #2 were also observed. The test PK values for subject #2 were higher in the original study but they were lower in the repeat study than the corresponding reference values (effect is much prominent in case of C_{max}).

The result presented in Table 1 indicated that in the case of clomipramine, the changes in **AUC_{0-t}** for A and B between the original and repeat assays were 55% and 71% for subject #22 and subject #30, respectively. The changes in **AUC_{0-inf}** for A and B between these two assays were 54% and 72% for subject #22 and subject #30, respectively. The changes in **C_{max}** for A and B between the original and repeat assays were 59% and 55% for subject #2 and subject #30, respectively. In the case of monodesmethylclomipramine, besides the changes in **AUC_{0-t}**(84%) and **AUC_{0-inf}** (78%) for subject #30, changes in **C_{max}** for A and B between these two assays were also observed to be 55% and 56% for subject #2 and subject #30, respectively.

These results clearly indicated that the repeat assay altered the PK parameters significantly not only for subject #30, but also for other subjects, and on the basis of these variable data, it is not possible to accept the repeat PK values of subject #30 as his actual values. Hence, subject #30 could not be treated as an outlier, and therefore, the fasting study remained unacceptable.

The Bioequivalence Study under Fed Conditions:

The sponsor has stated in the clinical report that, of 18 male volunteers (group I) who originally enrolled in the study, six subjects (#4, #9, #13, #14, #17, #18) did not complete the study. The firm has also stated that, 3 subjects of 6 additional subjects enrolled (group II) could not complete the study. Thus a total of 15 subjects completed the study (1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 15, 16, 19, 22, 23). The firm has also specified in the protocol (Project No. 940494) under the "statistical Analysis" section that subjects who vomited within 24 hours of

drug administration were to be excluded from the analysis, and consequently, subjects No. 22 and 23 should be excluded from the fed study. Hence, the total number of subjects completing the study should be 13.

Furthermore, the sponsor had reported (attached memo in Appendix #3) that clomipramine levels were not estimated correctly from plasma samples of subject #3. This subject's concentration data is therefore incomplete and his data was excluded from statistical and pharmacokinetic analysis. Therefore, both the pharmacokinetic and statistical analysis should be conducted on plasma data of 12 and 13 subjects for clomipramine and monodesmethylclomipramine, respectively.

However, the results of the fed study submitted by the sponsor previously as well as submitted in the current amendment (Appendix #4, attached) were derived from 16, 15 , 14 and 12 subjects' plasma data without providing any explanation. These results are not acceptable to the Division of Bioequivalence, and consequently, the bioequivalence study under fed conditions on Clomipramine Hydrochloride, 25 mg capsules remained unacceptable.

Deficiency/Comments:

1. Subject #30 does indeed have unusual values, but he is not the only subject with unusual values. One of the reasons is that there is significant intersubject variability due to genetic polymorphism which occurs for the enzymes responsible for hydroxylation of clomipramine and monodesmethylclomipramine. However, the unusual AUC_{0-t} value for the metabolite of Subject #30 appeared to be due to the fact that there were only five non-zero measured concentrations. The repeat study (P#920438A) indicated that the pharmacokinetic parameter levels of subject #30 following the redosing of the test and reference products were more similar as opposed to the original study (P#920438) where the test levels of subject #30 were considerably lower than the reference levels (both in parent compound and in metabolite). However, the question still remained unresolved, why there were only 5 measurable concentrations for metabolite of subject #30 on the test product in the original study. If the individual is a slow metabolizer than other subjects, the concentrations of the parent compound would be higher than the corresponding

levels of other subjects in the earlier time points. But it was reported in the original study that for AUC_{0-t} of the parent compound, A/B% (A=test, B=reference) was only 28.6, whereas the mean A/B% of all 32 subjects was 102.07. If the metabolism rate is slow, the metabolite would be seen at the later time points, and not at the earlier time points. Furthermore, if the metabolite levels really dropped below the LOQ after 12 hours, the question would be, why did that happen with the test product only and also, only in the original study but not in the repeat study.

2. The decision as to whether the bioequivalence of the test and reference products should be assessed on the original data for 33 subjects, or on the data excluding subject #30, requires biochemical, physiological and pharmacological judgements as well as statistics.

3. The statistician at the Agency has conducted an analysis on the plasma data (Project #920438A) of four additional subjects (repeat) as a stand-alone study. Although they surprisingly passed for AUC_{0-t} and $AUC_{0-inf,}$ they failed for C_{max}. This indicates, though the regression analysis conducted by the firm on these repeat study data of four subjects meets the criterion for AUC_{0-t} (metabolite), it will probably fail for C_{max} (firm did not provide analysis for AUC_{0-inf} and $C_{max)}$. The firm should submit regression curves for all three parameters, AUC_{0-t}, AUC_{0-inf} and C_{max} for both metabolite and parent compound.

4. The repeat study (P#920438A) indicated that the pharmacokinetic (PK) parameter levels of subject #30 following the redosing of the test(A) and reference(B) products were more similar as opposed to the study P#920438 (original) where the test levels of subject #30 were considerably lower than the reference levels. However, it should be noted here that a similar result in the case of subject #22 and an opposite result in subject #2 were also observed. The test PK values for subject #2 were higher in the original study but they were lower in the repeat study than the corresponding reference values (effect is much prominent in case of C_{max}).

5. The results of the original and repeat studies indicated that <u>in the case of clomipramine</u>, the changes in AUC_{0-t} for A and B between the original and repeat assays were 55% and

71% for subject #22 and subject #30, respectively. The changes in AUC_{0-inf} for A and B between these two assays were 54% and 72% for subject #22 and subject #30, respectively. The changes in C_{max} for A and B between the original and repeat assays were 59% and 55% for subject #2 and subject #30, respectively. In the case of monodesmethylclomipramine, besides the changes in AUC_{0-t} (84%) and AUC_{0-inf} (78%) for subject #30, changes in C_{max} for A and B between these two assays were also observed to be 55% and 56% for subject #2 and subject #30, respectively. These results clearly indicated that the repeat assay altered the PK parameter values significantly, not only for subject #30, but also for other subjects, and on the basis of these variable data, it is not possible to accept the repeat PK values of subject #30 as his actual values. Hence, subject #30 could not be treated as an outlier, and therefore, the fasting study remained unacceptable.

6. As clomipramine is a highly variable drug, it could also be argued that, based on the large inter-subject variability, it would have been possible that some other subject would have shown more difference, had the study, (P#920438A) was conducted redosing all 33 subjects.

7. Furthermore, it could also be argued that, since there is large inter-study variation in levels, the redosed subjects may possibly give different levels if dosed for the third time.

8. In conclusion, the Agency is not convinced of the firm's claim about fasting study bioequivalence. Based on the provided information and failure of $LnAUC_{0-t}$ of monodesmethylclomipramine for 90% confidence interval, the test product cannot be considered bioequivalent to the innovator product.

9. The firm had indicated in the original report (dated September 19, 1995) as well as in the current amendment (dated January 20, 1997), that the total number of subjects completed the fed study were 15 (N1=12, N2=3, in two groups). As specified in the protocol (Project No. 940494) under the "statistical Analysis" section, subjects who vomited within 24 hours of drug administration were to be excluded from the analysis, and therefore, on that basis, subjects No. 22 and 23 should be excluded from the fed

study. Hence, the total number of subjects completing the study should be 13. Furthermore, the sponsor had reported (attached memo in Appendix #3) that clomipramine levels were not estimated correctly from plasma samples of subject #3. This subject's concentration data is therefore incomplete and his data was excluded from statistical and pharmacokinetic analysis. Therefore, both the pharmacokinetic and statistical analysis should be conducted on plasma data of 12 and 13 subjects for clomipramine and monodesmethylclomipramine, respectively. However, the results of the fed study submitted by the sponsor previously as well as submitted in the current amendment were derived from 16, 15 , 14 and 12 subjects' plasma data without providing any explanation (Appendix #4, attached). These results are not acceptable to the Division of Bioequivalence, and consequently, the bioequivalence study under fed conditions on Clomipramine Hydrochloride, 25 mg capsules remained unacceptable.

Recommendations:

1. The in vivo Bioequivalence studies conducted (under fed and fasted conditions) by Chelsea Laboratories, Inc. on its 25 mg Clomipramine Hydrochloride Capsules, Lot # 2216 SO versus the listed reference product, Anafranil[R] Capsule, 25 mg, manufactured by Basel Pharmaceuticals have been found to be unacceptable by the Division of Bioequivalence for the reasons stated in Deficiency/Comments #1 - #9 above.

2. The waiver of in vivo bioequivalence study on Clomipramine Hydrochloride 50 mg and 75 mg Capsules has been denied.

/S/

Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG See the note attached

Concur: ---------- Date:----------
Rabindra Patnaik, Ph. D.
Acting Director, Division of Bioequivalence

cc: ANDA # 74-751 (original, duplicate), HFD-650 (Director), HFD-652 (Huang, Pradhan), Drug File, Division File.
SP/10-27-97/X:\New\firmsam\74751SA.197

Team Leader's comment on Chelsea's clomipramine capsule (ANDA 74-751) amendment review:

Regarding the repeat study:

If we accept the notion that a firm has the option for redosing the subject when there is no readily available explanations for very low/or high results on test/or reference products, then we should focus on the objective of the follow-up study, which is to determine whether the same subject (with a small number of subjects serving as control) would exhibit extreme differences when redosed with the test and reference products. The data presented in Table 1 of this amendment review, especially those of subject #30, clearly showed that Test and Reference products now have more comparable values in all the pharmacokinetic parameters evaluated for not only the metabolite (which is the reason for the follow-up study) but also the parent drug. Although changes, in a smaller degree, in the control subjects were also observed (such as Cmax for the metabolite and parent drug in subject #2 and AUC for parent drug in subject #22), one would argue that their T/R ratios are within the ranges observed in the original study and the individual AUC or Cmax values are not too much deviated from the mean values, this is consistent with the variability observed for this drug product. Based on this, the team leader would recommend the Division to consider accepting the firm's request to exclude subject #30 from the statistical analysis of the original study and accept the fasting bioequivalence study.

Regarding the food study, it is still incomplete as recommended by the primary reviewer in this amendment review.

Concur: /S/ 12/22/97

/S/ , 12/20/97
Yih-Ghain Huang, Ph.D.

Concur/Do not Concur: /S/ 12/23/97
Dale Conner, Ph. D.
Director, Division of Bioequivalence.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74751

CORRESPONDENCE

Clomipramine Hydrochloride Capsules
ANDA 74-751

JUL 31 1996

Chelsea Laboratories, Inc.
Attention: Lorraine W. Sachs
896 Orlando Avenue
West Hempstead, NY 11552

Dear Ms. Sachs:

Reference is made to the Abbreviated New Drug Application dated September 19, 1995 and the amendment submitted on May 28, 1996 for Clomipramine Hydrochloride Capsules, 25 mg, 50 mg and 75 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The fasting and non-fasting in vivo bioequivalence studies fail to satisfy the appropriate bioequivalence criteria.

   a. The 90% confidence interval (CI) for log-transformed AUC_{0-t} of %, is not within the acceptable range of %, for the metabolite, monodesmethyl-clomipramine.

   b. The non-fasting study, conducted with 16 subjects, does not meet the bioequivalence criterion of ±20% difference between the pharmacokinetic parameter AUC_{0-t} (using of the test and reference products for clomipramine.

2. Exclusion of data from subject #30 (fasting study) is not acceptable, without proper justification.

   The guidance "Statistical procedures for bioequivalence studies using a standard two-treatment crossover Design" (July 1992) indicates that if a subject is to be deleted from the analysis as an "outlier," justification must be provided. This justification is to be based on valid scientific reasons; statistical reason alone are not sufficient.

   Why were there only 5 measurable concentrations for the metabolite of subject #30 for the test product. If the metabolite levels really dropped below the LOQ, after 12 hours, the question remains, why did this occur with the test product only?

3. In addition to the major issues listed above the following comments should be taken into consideration:

   a. In separate analysis, the data of subjects 22 and 23 (fasting study) were excluded on the basis of vomiting within 24 hours of drug ingestion and the pharmacokinetic parameters of clomipramine but not monodesmethyl-clomipramine were recalculated. This action is only acceptable if this was an exclusion criterion specified in study protocol. However, subject's 22 and 23 data should be excluded from all analyses, (i.e., both parent compound and metabolite).

   b. An explanation for the use of residual effects (RESIDA and RESIDB) in the statistical model, should be provided.

   c. The period designation should reflect the actual day that a treatment was received. If there were add-on subjects, then there should be more than three levels of PERIOD in a three-way-crossover study design. The period should always be examined, even though all blood samples were assayed together. In this study, Group I started on Feb. 22, 1995 and three weeks later, Group II started on April 21, 1995. The preferred Model for statistical analysis of this study should be:

      Model Y = Seq Subj(Seq) Per Group*Per Trt;

      The analysis should permit testing for the possibility that the period effect for Group I was different from the period effect for Group II.

   d. There was no verbal explanation in the result section. Please present the study data with proper explanations in future submissions.

   e. The Office recommends that all non-fasting studies be designed to ensure that at least 18 subjects complete the study.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be considered to be a MAJOR-amendment and will be required to address all of the comments presented in this letter.

Should you have any questions, please call Jason A. Gross, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-751

MAR 15 1996

Chelsea Laboratories, Inc.
Attention: Ernest E. Lengle, Ph.D.
8606 Reading Road
Cincinnati OH 45215-0686

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on September 19, 1995, for Clomipramine Hydrochloride Capsules 25 mg, 50 mg, and 75 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The following is required for review:

   a. The extraction and derivatization procedures of clomipramine and monodesmethylclomipramine from human plasma before injecting into the

   b. The analytical conditions.

   c. The Lot size of the test product on which the *in vitro* dissolution testing and *in vivo* bioequivalence study were conducted.

   d. The data on monodesmethylclomipramine levels and the corresponding pharmacokinetic parameters of the test and reference products of the study conducted under fed condition.

2. Monodesmethylclomipramine levels of the test and reference products are comparable in the study conducted under fasting condition. However, in some subjects, the carryover effect was observed in Period II. The statistical analysis on monodesmethylclomipramine data was not performed; therefore, the Agency requirement for approval is not met

3. The comparative *in vitro* dissolution testing conducted on 25.0 mg, 50 mg and 75.0 mg Clomipramine Hydrochloride Capsule is not acceptable. The dissolution testing should be conducted using the following dissolution conditions:

Apparatus:	USP 23 Apparatus II (Paddle)
Speed:	RPM 50
Medium:	500 mL 0.1N HCl at 37°C
Tolerances:	% (Q) in 30 minutes
Analytical Procedure:	UV Absorption at ca. 252 nm.

4. In the submission it was specified that you had information which indicates that AUC and Cmax increase as a linear function of dose between 25 and 75 mg, please submit this data for review. This was previously requested during a telephone call on February 9, 1996, between Ernest Lengle (Chelsea) and Jason Gross (OGD), and has not yet been received.

5. In addition, the waiver request for the test product should be resubmitted when responding to the above deficiencies.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Deputy Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department

P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

NDA ORIG AMENDMENT
N/A

Mail No.: 98-112

September 10, 1998

Douglas L. Sporn
Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Clomipramine HCl Capsules, 25 mg, 50 mg, and 75 mg
ANDA 74-751
Telephone Amendment

Dear Mr. Sporn:

This is in response to the FDA telephone conversation on September 1, 1998 for the above mentioned ANDA application. For ease of review, your comments are in bold text followed by our response.

1. **The Division of Chemistry request that the Quantitative Composition Statements for the 25 mg, 50 mg and 75 mg (i.e. pages 80, 90, and 91 of the September 19, 1995 submission) be revised.**

   Pregelatinized Starch NF (Starch 1500) is
   manufacturing process. Chelsea's practice was to list quantities for the starch which corresponded to information on the batch records and to the amount needed for in the manufacturing process. This approach agrees with the Flow Diagram listed on page 248 and the proposed Master Batch Records (see pages 257 and 259, 273 and 275, and 289 and 291 for the 25 mg, 50 mg and 75 mg strengths, respectively). However, in the Qualitative Composition Statements, Pregelatinized Starch is mentioned only once.

   In compliance with FDA's request, only one quantity of Pregelatinized Starch NF (Starch 1500) is given in the revised Quantitative Composition Statements for the Clomipramine Capsules (see attachments).

2. On page 389 of the September 19, 1995 submission, the following statements are made:
Samples are taken representing the top, middle and bottom portions of the blend. These samples maintain the integrity of each sample position at all times for blend uniformity." What is the size of the quantity taken from each sample position?

Chelsea's policy at the Monroe, NC. facility in 1994 (when the submission batches were made) was to routinely remove approximately 25 g of the final blend from the top, middle and bottom of each storage drum for in-process analysis. For in-process blend assay testing, approximately 200 mg sample sizes were removed from the 25 g aliquot [see pages 401 and 402 (sample weight data)] for analysis. Since the three dosage strengths have a common blend, the 200 mg samples size corresponds to a unit sample dose of the 50 mg strength drug product.

Chelsea commits that for future commercial batches, approximately 1 gram will be removed for in-process blend assay analysis. This is equivalent to either three, five, or ten times the sample size for the three dosage strengths. Addition samples will be taken for particle size determination.

We believe that all comments made by the FDA have been addressed. If there are any questions regarding the response, please call me at (513) 948-3149.

Sincerely,

Ernest Lengle, Ph.D.
Director
Regulatory Affairs

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department

P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No.: 98-098

NEW CORRESP
NC

August 10, 1998

Douglas L. Sporn
Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Dear Mr. Sporn:

Re: Clomipramine Hydrochloride Capsules, 25 mg, 50 mg, and 75 mg
ANDA 74-751

Dear Mr. Sporn:

Chelsea Laboratories, Inc. wishes to withdraw its December 18, 1997, amendment to our unapproved application for Clomipramine HCl Capsules, 25 mg, 50 mg, and 75 mg (ANDA 74-751) in compliance with 21 CFR 314.96. The December 18, 1997, amendment regarded the transfer of the manufacturing capabilities for this drug product from Monroe, NC to a manufacturing facility located in Our decision to withdraw this amendment is made without prejudice to refilling.

Sincerely,

Ernest Lengle, Ph.D.

Ernest Lengle, Ph.D.
Director
Regulatory Affairs

cc: Mr. Joseph Buccini, FDA

RECEIVED
AUG 12 1998
[illegible]

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department

P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No.: 98-091
July 6, 1998

BIOAVAILABILITY

ORIG AMENDMENT
N/A's

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
OGD, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Clomipramine HCl Capsules, 25 mg, 50 mg, and 75 mg
ANDA 74-751
Biowaiver Request Amendment

Dear Dr. Conner:

In accordance with 21 CFR 320.22(d)(2) and per our recent telephone conversation with Ms. Lizzie Sanchez, Chelsea Laboratories, Inc. is requesting a "Waiver of Evidence of In-vivo Bioavailability" for Clomipramine Hydrochloride Capsules, 50 mg and 75 mg.

Clomipramine Hydrochloride Capsules, 50 mg and 75 mg conform to all applicable requirements of the 21 CFR 320.22 (d)(2) citation, i.e.:

"The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product made by the same manufacturer and the following conditions are met."

(i) "The bioavailability of the other product has been demonstrated."
(ii) "Both drug products meet an appropriate in vitro test approved by the Food and Drug Administration."
(iii) "The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients."

The Bioavailability Study was performed comparing Chelsea's Clomipramine Hydrochloride Capsules, 25 mg to Basel Pharmaceuticals (Anafranil®) 25 mg Clomipramine Hydrochloride Capsules. This study was submitted to FDA in the original application dated September 19, 1995.

If there are any questions regarding this amendment, please call me at (513) 948-3149.

Sincerely,

Ernest Lengle, Ph.D.
Director, Regulatory Affairs

RECEIVED
JUL 07 1998
GENERIC DRUGS

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department

P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No.: 98-028

February 27, 1998

N/AB

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
OGD, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Clomipramine HCl Capsules, 25 mg, 50 mg, and 75 mg
ANDA 74-751
Bioequivalency Amendment

Dear Dr. Conner:

This is in response to the FDA deficiency letter dated January 2, 1998, for the above mentioned ANDA application. For ease of review, your comments are in bold text followed by our response.

1. **The Division of Bioequivalence has no further questions regarding the fasting study at this time.**

   Noted

2. **You have indicated in the original report (dated September 19, 1995) as well as in the current amendment (dated January 20, 1997), that the total number of subjects completing the fed study were 15 (n1 = 12, n2 = 3, in two groups). As specified in the protocol (Project No. 940494), under the "Statistical Analysis" section, subjects who vomited within 24 hours of drug administration were to be excluded from the analysis, and therefore, on that basis, subjects No. 22 and 23 should be excluded from the fed study. Hence, the total number of subjects completing the study should be 13.**

   Since comments #2 and #3 are related, both have been addressed below.

3. **Furthermore, you have reported that clomipramine levels were not estimated correctly from plasma samples of subject #3. This subject's concentration data is therefore incomplete and his data was excluded from statistical and pharmacokinetic analysis. Therefore, both the pharmacokinetic and statistical analysis should be conducted on plasma data of 12 and 13 subjects for clomipramine.**

monodesmethyl-clomipramine, respectively. However, the results of the fed study submitted previously, as well as the study submitted in the current amendment were derived from 16, 15, 14 and 12 subjects' plasma data without providing any explanation. These results are not acceptable to the Division of Bioequivalence, and consequently, the bioequivalence study under fed conditions on Clomipramine Hydrochloride, 25 mg capsules remains unacceptable.

Please refer to Tables 1 and 2, respectable, for a summary of subject data used for clomipramine and monodesmethyl-clomipramine analyses.

Subjects No. 4, 9, 13, 14, 17 and 18 (Group 1) and 20, 21 and 24 (Group 2) did not complete the study (i.e., they did not complete all three clinical phases). Therefore, 15 of the 24 subjects enrolled completed all three periods of the study (12 of 18 from Group 1 and 3 of 6 from Group 2).

The "Statistical Analysis" section of the protocol specifies, "Data from only those subjects who completed at least two periods of the study will be submitted for statistical analyses, with unbalanced groups being used if necessary. In addition, statistical analyses will be performed excluding those subjects who vomited or experienced diarrhea within 24 hours of drug administration." Later in the same section, the protocol specifies, "The comparisons of interest are: B vs. A and B vs. C".

Thus, although Subject No. 14 and 24 did not complete the study, they completed Regimens B and C, and B and A, respectively (the comparisons of interest as defined in the protocol). Therefore, samples from these subjects were analyzed.

Subject No. 4 completed two periods of the study, Regimens A and C. The A vs. C comparison was not specified in the protocol as a comparison of interest. Therefore, samples from this subject were not analyzed.

To summarize so far, of the 24 subjects dosed, 6 did not complete at least 2 periods and 1 did not complete at least 2 regimes of interest, thereby leaving 17 subjects whose plasma samples were analyzed.

Of these 17 subjects, one had incomplete clomipramine data. Clomipramine concentration data for Subject No. 3 were incomplete due to repeated analytical rejection of the standard curves; therefore, his data were excluded from pharmacokinetic and statistical analyses.

Clomipramine

In compliance with the protocol, two data sets for clomipramine were presented in the report dated August 16, 1995: 1) containing data for all subjects completing at least two

periods of the study [where the dosing regimens were either B and C or B and A, the comparisons of interest] (i.e., n = 16) and 2) excluding data form Subject No. 22 and 23 who vomited (i.e., n = 14). The latter is considered the definitive dataset.

In the response (dated January 17, 1997) to the FDA deficiency letter, additional statistical analyses were performed on data from the first group of subjects completing the study (n = 12) in order to assess period effects. Since both sets of data had no significant period effect, it was concluded that there was no significant difference in period effect for both groups. Results of these analyses were presented in Appendix 3 of the response dated January 17, 1997.

Monodesmethyl-clomipramine

The protocol specified that plasma modesmethyl-clomipramine concentrations at each sampling time, together with means, standard deviations and coefficients of variation would be reported. In the report dated August 16, 1995, these data were provided in Tables D10-D12. Data from Subjects No. 22 and 23 were included (i.e., n = 17).

In response to the FDA deficiency letter, statistical analysis was performed on the metabolite data with Subject No. 22 and 23 excluded (i.e., n = 15). Results of these analyses were present in Appendix 3 of the response dated January 17, 1997.

To summarize:

1) The original report (dated August 16, 1995) correctly identifies the number of subjects completing the study (all three periods) as 15. The response (dated January 17, 1997) to an FDA deficiency letter was consistent with the original report in this respect.

2) In the original report, in compliance with the protocol, two data sets containing data for all subjects completing at least two periods of interest (excluding data for Subject No 3) were presented for clomipramine: 1) all data, n = 16; and, 2) excluding subjects who vomited, n = 14. The latter was the definitive data set.

3) As specified in the protocol, the original report presented descriptive data only for monodesmethyl-clomipramine for all subjects completing at least two periods of interest, including data from subjects who vomited (n = 17). The response to the FDA deficiency letter presented results of statistical analysis for data excluding subjects who vomited (n =15). The latter can be considered the definitive data set.

4) In the response to the FDA deficiency letter, additional statistical analyses were performed on data from the first group of subjects completing the study (n = 12) in order to assess period effects.

We believe that all comments made by the FDA have been addressed. If there are any questions regarding the response, please call me at (513) 948-3149.

Sincerely,

Ernest Lengle, Ph.D.
Director
Regulatory Affairs

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department

P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No.: 97-230

NDA ORIG AMENDMENT

December 18, 1997

Douglas L. Sporn, Director
OGD, CDER, FDA
Document Control Room
Metro Park North, Building II
7500 Standish Place
Rockville, MD 20855

RE: ANDA 74-751
Clomipramine HCl Capsules, 25 mg, 50 mg and 75 mg

Dear Mr. Sporn:

References are made to Chelsea Laboratories, Inc.'s Abbreviated New Drug Application for Clomipramine HCl Capsules, 25 mg, 50 mg and 75 mg (ANDA 74-751) and to the SUPAC-IR Guidance. Although this application is awaiting approval by OGD, we are requesting approval for the following proposed site and manufacturing changes based on the SUPAC-IR guidance. In addition, we are requesting approval for additional container/closure systems due to the change in the manufacturing site. These changes, however, will not affect any analytical test methods/specifications, trade dress of the drug product (shape, size, color, logo, etc.), or approved vendor of the drug substance. Chelsea Laboratories, Inc. will retain responsibility for this ANDA.

SITE CHANGE

In compliance with the SUPAC-IR Guidance, Chelsea Laboratories, Inc. (a subsidiary of Hoechst Marion Roussel [HMR]) is notifying FDA of the transfer and consolidation of its manufacturing, testing and packaging operations from its currently approved facility located at 2021 E. Roosevelt Blvd., Monroe, North Carolina (Reg. No. 1038928) to an equivalent HMR manufacturing facility located at 2110 E. Galbraith Road, Cincinnati, Ohio (Reg. No. 1510437). The Cincinnati facility is in satisfactory GMP compliance based on an inspection concluded on December 5, 1995. No 483 observations were issued following this inspection. This change corresponds to a Level 2 Change as described in Section IV of the Guidance.

RECEIVED
DEC 19 1997
GENERIC DRUGS

CHANGE IN BATCH SIZE

Chelsea Laboratories, Inc. is proposing changes in the batch sizes: for Clomipramine HCl Capsules, 25 mg from M capsules (150 kg) to M capsules (100 kg); for Clomipramine HCl Capsules, 50 mg from M capsules (150 kg) to M capsules (100 kg); and for Clomipramine HCl Capsules, 75 mg from M capsules (99.9 kg) to M capsules (100 kg). These changes correspond to a Level 1 Category: Changes In Batch Size as described in Section V of the SUPAC-IR Guidance.

CHANGE IN MANUFACTURING

The blending operations were changed from
to : . In the "Unit Operation - Blending and Mixing" section of the "Equipment Sameness, Draft Guidance for Industry" issued February 3, 1997 (a collaborative draft issued by FDA and the International Society of Pharmaceutical Engineers), . These changes in manufacturing equipment correspond to a Level 1 Category: Manufacturing Equipment Change as described in Section VI.A.1 of the SUPAC-IR Guidance.

SUPPORTING DATA

To support these changes, we have enclosed three months accelerated stability data on the transferred drug product. In addition, we have performed multi-point dissolution profiles in the compendial media for the currently approved and transferred drug products; data are submitted for review.

We commit that at least one lot of the transferred drug product will be placed in the stability program. Initial stability data is provided in this application. Long-term stability data for this lot will be reported in the annual report. All analytical testing of the stability test samples will be performed at the Cincinnati, Ohio facility (the transfer site) when commercial distribution of drug product from this facility is initiated.

SUMMARY

Based on the SUPAC-IR Guideline, Chelsea Laboratories, Inc. is requesting approval for the aforementioned site and manufacturing changes. Data to support these changes are submitted for review. The analytical methods used at the new site are identical to current approved methods with the exception of site dictated formatting and method numbering systems.

All proposed changes are a direct result of the change in the location of the manufacturing facility. The Cincinnati facility will use similar operating equipment, SOPs, environmental conditions and controls as compared to those described in the approved application. The manufacturing batch record format has been modified to reflect new administrative information and the location of the new site. The batch

record, stability reports and comparative dissolution data for the current and transferred drug products are enclosed in support of this submission.

NON-SUPAC IR CHANGE

Chelsea Laboratories is also requesting approval for additional container/closure systems for the application. To support this request, we have included accelerated and room temperature stability data for the drug product packaged in the proposed container/closure systems. These changes are due to the change in the manufacturing facility.

Chelsea continues to be committed to manufacturing safe and effective drug products and will make every effort to ensure that the same high quality product standards are maintained at the Cincinnati facility.

Chelsea also certifies that, concurrently with the sending of this information, a true copy of this amendment (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to the manufacturing facility's district office (Cincinnati, Ohio).

If there are any questions regarding this submission, please call me at (513) 948-3149 or by FAX (513) 948-7083.

Sincerely,

Ernest Lengle, Ph.D.
Chelsea Laboratories, Inc.
Director, Regulatory Affairs

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department

P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No.: 97-150

August 20, 1997

NEW CORRESP
BIOAVAILABILITY

FOR BIO REVIEW
J Bucci 8/25/97

Rabindra N. Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
OGD, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Clomipramine HCl Capsules, 25 mg, 50 mg, and 75 mg
ANDA 74-751
Telephone Amendment

Dear Dr. Patnaik:

Chelsea Laboratories, Inc. was recently informed by the Department of Bioequivalence that our computer disks contained only the raw data for the plasma levels for the two biostudies submitted in support of this application. The Department has requested that additional computer disks be submitted containing the calculated pharmacokinetic parameters.

Enclosed please find three computer disks. The first disk contains the data for the plasma levels and the accompanying calculated pharmacokinetic parameters for the original fasted study (Project No. 920438). The second disk contains the data for the plasma levels and the accompanying calculated pharmacokinetic parameters for the original fed study (Project No. 940494). The third disk contains the data for the plasma levels and corresponding calculated pharmacokinetic parameters for a redosing fasted study (Project No. 920438A). Each disk contains two files. The FDA.1 file contains the information for the Clomipramine; the FDA.2 file contains the information for the Monodesmethylclomipramine.

At the Department's request, a copy of each disk is being sent directly to Ms. Lizzie Sanchez, Project Manager for the Department of Bioequivalence.

We are sorry for any inconvenience this omission may have caused. We believe that all comments made by the FDA have been addressed. If there are any questions regarding this response, please call me at (513) 948-3149.

Sincerely,

Ernest Lengle, Ph.D.

Ernest Lengle, Ph.D.
Director, Regulatory Affairs

RECEIVED
AUG 20 1997
GENERIC DRUGS

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department

P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No.: 96-181

NDA ORIG AMENDMENT

N/AC

December 17, 1996

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
HFD-620 Room 204, Office of Generic Drugs
Metro Park North, Building 2
7500 Standish Place
Rockville, MD 20855

Subject: Clomipramine Hydrochloride Capsules 25 mg, 50 mg, 75 mg
ANDA 74-751
Major Amendment

Dear Dr. Patel:

This is in response to an FDA deficiency letter dated August 16, 1996 for the above-mentioned ANDA. For ease of review, your comments are in bold text followed by our response.

1. **Based on your submitted data, please revise your specifications for the release of the finished drug product and stability regarding impurities/related substances and degradation products to NMT % total (including imipramine hydrochloride).**

   The Finished Product and Stability Methods and Specifications, as well as the Raw Material Methods and Specifications, have been revised as you requested. A copy of each Specification is included.

2. **We are waiting for your response to our bio deficiency letter dated July 31, 1996.**

   A response to the bio deficiency letter is being prepared and it will be submitted soon.

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to our manufacturing facility's district office (Atlanta, Georgia). This "field copy" was contained in burgundy binders.

We believe that all comments made by the FDA have been addressed. If there are any questions regarding this response, please call me at (513) 948-3149.

Sincerely,

Ernest E. Lengle, Ph.D.
Director, Regulatory Affairs

Enclosures

RECEIVED
DEC 23 1996
GENERIC DRUGS

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department

P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No.: 96-073

May 28, 1996

Rabindra N. Patnaik, Ph.D.
Deputy Director, Division of Bioequivalence
Office of Generic Drugs
CDER / FDA / HSD-630
Metro Park North II
7500 Standish Place, Room E130
Rockville, MD 20855

Subject: Clomipramine Hydrochloride Capsules 25 mg, 50 mg, 75 mg
ANDA 74-751
Minor Amendment

Dear Dr. Patnaik:

This is in response to an FDA deficiency letter dated March 15, 1996, for the above-mentioned ANDA. For ease of review, your comments are in bold text followed by our response.

1. The following is required for review:

a. The extraction and derivatization procedures of clomipramine and monodesmethylclomipramine from human plasma before injecting into the

The bioequivalence study was performed by
The responses provided from are found in Attachment 1.

b. The analytical conditions.

The responses provided from are found in Attachment 1.

c. The Lot size of the test product on which the *in vitro* dissolution testing and *In vivo* bioequivalence study were conducted.

The *in vivo* bioequivalence study was conducted on the 25 mg strength of Clomipramine Hydrochloride Capsules, Lot # 2216SQ. The batch size was capsules. The *in vitro* dissolution testing was performed on all three strengths of capsules.

Strength	Lot Number	Batch Size
25 mg	2216SQ	capsules
50 mg	2217SQ	capsules
75 mg	2218SQ	capsules

d. The data on monodesmethylclomipramine levels and the corresponding pharmacokinetic parameters of the test and reference products of the study conducted under fed condition.

The responses provided from are found in Attachment 1.

2. Monodesmethylclomipramine levels of the test and reference products are comparable in the study conducted under fasting condition. However, in some subjects, the carryover effect was observed in Period II. The statistical analysis on monodesmethylclomipramine data was not performed; therefore, the Agency requirement for approval is not met.

The responses provided from are found in Attachment 1.

3. The comparative *in vitro* dissolution testing conducted on 25.0 mg, 50 mg, and 75.0 mg Clomipramine Hydrochloride Capsule is not acceptable. The dissolution testing should be conducted using the following dissolution conditions:

Apparatus:	**USP 23 Apparatus II (Paddle)**
Speed:	**RPM 50**
Medium	**500 mL 0.1N HCl at 37°C**
Tolerances:	**% (Q) in minutes**
Analytical Procedure:	**UV Absorption at ca. 252 nm.**

As requested, the dissolutions for all strengths for both the Chelsea product and the brand product have been performed using 0.1N HCl; 500 ml @ 37°C, USP #2 (Paddles), 50 rpm. The Chelsea Finished Product and Stability Specifications have been updated to reflect these new parameters. The results and the updated specifications are found in Attachment 2. Copies of these specifications were included in a minor amendment to the Chemistry Division, which was sent on May 23, 1996.

4. In the submission it was specified that you had information which indicates that AUC and Cmax increase as a linear function of dose between 25 and 75 mg, please submit this data for review. This was previously requested during a telephone call on February 9, 1996, between Ernest Lengle (Chelsea) and Jason Gross (OGD), and has not yet been received.

The information requested was sent on February 13, 1996. The information had not been forwarded to Jason Gross (OGD) prior to the mailing of the deficiency letter on March 15. On March 26, 1996 Sandra Middleton was contacted and she confirmed that the information had been located.

5. In addition, the waiver request for the test product should be resubmitted when responding to the above deficiencies.

Please see Attachment 3 for Request for Waiver of Evidence of In-vivo Bioavailability and a comparison of the formulation between the Chelsea Clomipramine Hydrochloride Capsules, 50 mg and 75 mg with the 25 mg bio-study strength.

We believe that all comments made by the FDA have been addressed. If there are any questions regarding this response, please call me at (513) 948-3149.

Sincerely,

Ernest E. Lengle, Ph.D.

Ernest E. Lengle, Ph.D.
Director, Regulatory Affairs

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department

P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No.: 96-181

NDA ORIG AMENDMENT

N/AC

December 17, 1996

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
HFD-620 Room 204, Office of Generic Drugs
Metro Park North, Building 2
7500 Standish Place
Rockville, MD 20855

Subject: Clomipramine Hydrochloride Capsules 25 mg, 50 mg, 75 mg
ANDA 74-751
Major Amendment

Dear Dr. Patel:

This is in response to an FDA deficiency letter dated August 16, 1996 for the above-mentioned ANDA. For ease of review, your comments are in bold text followed by our response.

1. **Based on your submitted data, please revise your specifications for the release of the finished drug product and stability regarding impurities/related substances and degradation products to NMT % total (including imipramine hydrochloride).**

   The Finished Product and Stability Methods and Specifications, as well as the Raw Material Methods and Specifications, have been revised as you requested. A copy of each Specification is included.

2. **We are waiting for your response to our bio deficiency letter dated July 31, 1996.**

   A response to the bio deficiency letter is being prepared and it will be submitted soon.

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to our manufacturing facility's district office (Atlanta, Georgia). This "field copy" was contained in burgundy binders.

We believe that all comments made by the FDA have been addressed. If there are any questions regarding this response, please call me at (513) 948-3149.

Sincerely,

Ernest Lengle, Ph.D.

Ernest E. Lengle, Ph.D.
Director, Regulatory Affairs

Enclosures

RECEIVED
DEC 23 1996
GENERIC DRUGS

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department

P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

September 19, 1995

Dr. Charles Ganley, Acting Director
Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA Clomipramine Hydrochloride Capsules 25 mg, 50 mg, and 75 mg

Dear Dr. Ganley:

Chelsea Laboratories, Inc. submits today an original abbreviated new drug application ("ANDA") seeking approval to market Clomipramine Hydrochloride Capsules 25 mg, 50 mg, and 75 mg that are bioequivalent to the listed drug, Anafranil®, manufactured by Basel Pharmaceuticals.

This ANDA consists of 22 volumes. Chelsea Laboratories is filing an archival copy (in blue binders) of the ANDA that contains all the information required in the ANDA, and a chemistry review copy (in red binders) which contains all the information in the archival copy with the exception of the Bioequivalence section (VI). A separate copy of the Bioequivalence section is provided in orange binders.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my numbers are 513-948-3149 (direct dial) and 513-948-7083 (fax).

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to our manufacturing facility's district office (Atlanta). This "field copy" was contained in burgundy binders.

Thank you for your prompt handling of this submission.

Sincerely,

Ernest E. Lengle, Ph.D.
Director, Regulatory Affairs